PROCEEDINGS
OF THE
ROYAL SOCIETY OF MEDICINE

Vol. 45 No. 4 April 1952

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Section of Endocrinology

President—A. W. SPENCE, M.D., F.R.C.P.

[*November* 28, 1951]

Miliary Tuberculosis in a Case of Acute Disseminated Lupus Erythematosus Treated with ACTH.—BETTY WALKER, M.A., M.B., B.S., M.R.C.P. (for N. G. HULBERT, M.A., M.D., M.R.C.P.).

Mrs. C. F., aged 35, housewife with two children.

1950: Onset of rheumatoid arthritis in *March*, affecting both hands and wrists; first seen in *May* when apical systolic murmur was also noted.

June: Butterfly eruption of acute lupus erythematosus on face.

August: Exacerbation of the arthritis; all joints except hips involved.

September 9: Admission to hospital; T. 99°–103° F. Rapid dissemination of lupus eruption on face, chest, upper and lower limbs occurred in the next two weeks (Fig. 1), associated with increasing anæmia, enlargement of the cervical, axillary and inguinal lymph nodes, albuminuria and red cell hæmaturia. The apical murmur had become louder, harsh and prolonged.

FIG. 1.—*September* 1950: Showing butterfly eruption and early dissemination on face, neck and chest.

FIG. 2.—*November* 1951: Lung fields showing miliary infiltration undergoing calcification.

FIG. 3.—*October* 1951: Showing normal freckled complexion; arrow denoting site of cold abscess of neck.

X-ray of chest normal. Hb 74–50%. W.B.C. 5,000 per c.mm. E.S.R. 38–75 mm. (Westergren). Serum proteins: Total 5·3 grammes per 100 c.c. Albumin 3·0 grammes, globulin 2·3 grammes per 100 c.c.

Blood urea: 30 mg. per 100 c.c. Blood culture sterile.

On this evidence, she was considered to be a case of acute disseminated lupus erythematosus with cardiac manifestations (Libman-Sacks syndrome). No response to salicylates, penicillin or blood transfusions.

November 14: Grossly emaciated, toxæmic and seemed unlikely to live. Treated with ACTH for eight or nine weeks; 50 to 200 mg. in four divided doses I.M. Total dose = 5·725 grammes. Immediate clinical response with defervescence and fall in pulse-rate, loss of pain and stiffness in affected joints. During the next month, the swelling of the joints subsided, the rash faded. Fever was controlled completely at the onset for three days, and for a further period of one week with increased dosage. She developed a moderate degree of moon face, became partially bald, and gained 5 kg. in weight in the first four weeks of treatment. Other signs of adrenal stimulation were an increase in the sodium-potassium ratio and a fall in the circulating eosinophils to zero. The white cell count showed a lymphopenia; the E.S.R. fell to 16 mm. in the first hour.

December 24, 1950 to *January* 3, 1951: Increasing fever, 99–104° F.

X-ray chest: Increased lung markings in the R. cardiophrenic angle.

January 17–19: Persistent fever 104–105° F. Considerable general deterioration but arthritis and

rash controlled. X-ray chest showed very numerous miliary deposits in both lung fields with early confluence of lesions.

C.S.F. normal. The ACTH was stopped and streptomycin, 2 grammes daily, begun. This dosage has been maintained. Auditory acuity began to diminish in early March but the clinical evidence of toxicity to the tuberculous process showed no signs of abating. By June she had become stone deaf. Adjuvant PAS was stopped after one month owing to intolerance.

May: Cold abscess R. forearm, drained in July, followed by two sinuses which healed by the beginning of October. Three other cold abscesses appeared August–October; sites: lower end of R. sterno-cleido-mastoid muscle; below outer aspect of R. knee-joint; in lower third of L. thigh.

November 6: X-ray chest showed miliary infiltrations undergoing calcification (Fig. 2). Her general condition has improved steadily (Fig. 3). The temperature and pulse have settled and she has gained 10 kg. in weight since July. The polyarthritis and lupus eruption are still in remission and the apical murmur has disappeared. Serum proteins: Total = 7·6 grammes per 100 c.c.; albumin 5·1 grammes ; globulin 2·5 grammes per 100 c.c. Proteinuria persists. Blood urea 50 mg. per 100 c.c. No tubercle bacilli have been isolated in films and cultures from the sputum or pus from abscesses.

Comment.—There is no doubt that ACTH therapy at the time of the acute lupus crisis was life-saving. It appears also to have induced an exceptionally long natural remission, but it is problematical whether actual recovery has yet occurred. Proteinuria persists and the blood urea has risen from 30 to 50 mg. per 100 c.c. 2 cases, however, have been reported in which treatment with cortisone produced increased albuminuria (Prunty, 1952; Jacobson, Heller and Hammarsten, 1951).

It was assumed that the miliary deposits in the lungs and elsewhere were tuberculous in origin, although tubercle bacilli were never isolated. Other cases of miliary tuberculosis, following ACTH and cortisone respectively and demonstrated post mortem, have been reported by Ferriman and Wilsdon (1950), Ferriman (1951) and Kleinschmidt and Johnston (1951). Proof is lacking that the hormones contributed to the development of miliary infection in these three instances, but the course of events suggests that it is a strong possibility. Why one patient should have survived is also a matter for conjecture. From experimental evidence, it appears that the influence of ACTH and cortisone may differ significantly in the different animal species. Hart and Rees (1950) and Michael *et al.* (1950) have shown that cortisone enhances the evolution of tuberculosis, even in those animals who possess a high natural resistance to the disease. On the other hand, Lurie *et al.* (1951) demonstrated that rabbits of high genetic susceptibility to tuberculosis react with certain of the pathological responses characteristic of naturally resistant rabbits when treated with cortisone.

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Dr. Raymond Greene: Although this patient has not been under my care I have seen her at frequent intervals during the last year or so.

Two points about her have seemed to me to be worth stressing. In the first place her chest was X-rayed as a precaution before treatment with ACTH was begun. In spite of the fact that the chest X-ray showed no evidence of pulmonary disease, the administration of ACTH apparently caused a miliary spread of a pre-existent tuberculous infection. We cannot be sure that this substance can safely be used even if the chest is apparently healthy.

In the second place we have the fact that this patient developed miliary tuberculosis from which she would certainly have died had it not been for treatment with streptomycin. As it is, she appears to be well on the way to complete recovery. In the future we shall presumably have a chemotherapeutic agent even more effective than streptomycin. When that time comes I think that we shall abandon the idea that ACTH should only be used when we can feel reasonably sure that no tuberculosis is present. I think that we shall employ it "of malice aforethought" in tuberculous cases as a means of exposing latent infection. We shall, as it were, use ACTH to set fire to the rick and stand round with "Neostreptomycin" to shoot the tubercle bacilli as they run out!

Diabetes Caused by ACTH Treatment of Rheumatoid Arthritis.—P. M. F. Bishop, D.M., M.R.C.P., and J. H. Glyn, M.B., M.R.C.P.

E. R., male, aged 31.

History.—Acute onset of rheumatoid arthritis 1948. Rapid spread to all joints in the body. Has steadily deteriorated since then. Many previous forms of treatment without any effect at all. Admitted to hospital in January 1951 bedridden and extremely crippled. No family history of diabetes. Urine was sugar free.

Treatment.—Six days' treatment with 25 U.S.P. units ACTH q.d.s. No clinical improvement. No metabolic changes except one urine specimen which was green to Benedict. He put on 3 lb. in weight.

Dose increased to 75 U.S.P. units, q.d.s. with immediate and dramatic clinical response. Urine: On second day, green reaction to Benedict; on fourth day, yellow reaction. Treatment was suspended on the seventh day, by which time symptoms of hypokaliemia had developed. During this period the metabolic changes were: Weight increase from 8 st. 1 lb. to 9 st. 1 lb. B.P. from 130/70 to 185/100. 17-ketosteroids from 4·35 to 9·1 mg./per 24 hours. E.S.R. from 88 to 40 mm. in the first hour (Westergren). Hb from 8·5 to 11 grammes %. R.B.C. from 3,600,000 to 4,700,000. Serum potassium from 18·4 to 13·4 mg.%. Serum sodium from 328 to 341 mg.%. Plasma proteins from 7·2 to 6·1 grammes %. Albumin: Globulin ratio changed from 0·8 : 1 to 1·2 : 1.

His glucose tolerance curve was as follows:

Fasting ..	139 mg./100 ml.	2 hours ..	220 mg./100 ml.
½ hour ..	151 ,,	2½ hours ..	197 ,,
1 hour ..	244 ,,	3 hours ..	151 ,,
1½ hours ..	220 ,,		

There was evidence of a lowered renal threshold.

From February 26 to April 11, 1951, he had no treatment. His clinical and metabolic state reverted to pre-treatment levels but he continued to have glycosuria and a further glucose tolerance test showed that he remained diabetic although his fasting blood sugar was not raised on this occasion:

Fasting ..	81 mg./100 ml.	1½ hours ..	300 mg./100 ml.
½ hour ..	127 ,,	2 hours ..	290 ,,
1 hour ..	174 ,,		

A glucose insulin tolerance test showed that he was insulin-sensitive at this time:

Fasting ..	116 mg./100 ml.	¾ hour ..	128 mg./100 ml.
¼ hour ..	116 ,,	1 hour ..	116 ,,
½ hour ..	116 ,,	1¼ hours ..	128 ,,

On April 11, 1951, daily doses of 100 mg. cortisone commenced. He has remained on a dose of between 75–100 mg. a day by mouth until the present time. Clinical response has been satisfactory; there have been no further side-effects. The diabetes is now relatively insulin-resistant and it is necessary to give 52 units soluble insulin twice a day and to restrict carbohydrate intake to 200 grammes daily. The relative effects of diet and insulin on his twenty-four-hour output of glucose are shown on the following table.

	100 grammes carbohydrates + 96 units insulin	Ordinary hospital diet + 96 units insulin	100 grammes carbohydrates without insulin	Ordinary hospital diet without insulin
24-hour output of glucose	10·9 grammes	24·5 grammes	96 grammes	161 grammes

Discussion

This patient had no symptoms which we considered to be relevant to his diabetes except for blurring of vision which fluctuated accurately in relation to his blood sugar. He showed no tendency to develop ketosis either before his insulin was started or at a later stage when insulin was temporarily withdrawn for experimental purposes.

It is too early yet to label this case permanent diabetes, especially as we do not know what would have happened to his carbohydrate metabolism if he had not started cortisone. There are, however, no signs as yet that the diabetes is abating.

The pathogenesis of this type of diabetes is not properly understood, but on theoretical grounds the following mechanisms may be suggested:

(1) The drugs are known to cause a reduction in the peripheral action of insulin by hexokinase inhibition and also to cause increased gluconeogenesis (Ingle, 1941). Both of these factors tend to produce hyperglycæmia, and hyperglycæmia alone can cause hydropic degeneration of the beta cells (Woerner, 1938; Lukens *et al.*, 1943) and this effect is enhanced in the presence of pituitary extracts.

(2) These drugs cause increased uric acid excretion (Forsham *et al.*, 1948). It has been suggested that an anomaly of the purine metabolism may produce alloxan-like metabolites which can cause beta-cell degeneration either directly on the beta cells or secondarily by reducing blood glutathione, since alloxan reacts with the S.H. groups of glutathione to form dialuric acid (Conn *et al.*, 1948).

(3) These drugs are known to reduce the blood glutathione (Conn *et al.*, 1948, 1949) and it is known that this substance has an important action in preventing beta-cell degeneration in experimental partially pancreatectomized animals exposed to diabetogenic stimuli (Lazarow, 1947).

(4) The stimulation of the alpha cells in the islets of Langerhans by ACTH, the secretions of these cells being diabetogenic (Heard *et al.*, 1948).

(5) The capacity of the renal tubules to reabsorb glucose is reduced by cortisone and ACTH.

(6) The ACTH may be contaminated with growth hormone or other diabetogenic anterior

pituitary hormones, but we think this unlikely because no case of diabetes in man from this cause has ever been confirmed.

The case was cared for and investigated by the Rheumatism Department of the West London Hospital and we wish to thank Drs. W. S. C. Copeman and O. Savage for permission to publish it. A more complete account has been published in the Annual Report of the Rheumatism Department of the West London Hospital (1951).

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Deficient Function of the Anterior Pituitary Associated with Hypertension, Steatorrhœa, Osteoporosis and Cutaneous Lesions.—ARNOLD BLOOM, M.D., and RAYMOND GREENE, D.M.

Miss V. S., aged 41.

History.—Patient was "born with rickets" and legs were in splints for two and a half years; she was unable to walk until 6 years old. "Backward at school." Took job as packer in a factory and remained there for twenty-two years. Never away ill. She has never menstruated. Fell and fractured right clavicle many years ago. Fractured right wrist four years ago. Three years ago had a stroke involving left side, good recovery. Nine months ago second attack, since when has been unable to get about. Admitted Whittington Hospital following third attack—pseudobulbar palsy—with some recovery.

Family history.—Only child. Parents, 6 aunts and uncles, all in good health.

On examination.—Skeletal: Ht. 4 ft. 7 in. (Lower 2 ft. 4 in. Upper 2 ft. 3 in.). Span 4 ft. 8 in. Malunited fracture R. clavicle. Genu valgum. Bilateral pes equinus cavus, L. in varus as well.

Skin: Single capillary nævus right leg; numerous pigmented macules, pigmented moles and fibromata on face (Fig. 1), trunk and limbs; petechiæ on chest.

Endocrine: Absent axillary hair; scanty pubic hair. Atrophic breasts and external genitalia.

Fundi: Medullated nerve fibres right disc. Moderate arteriosclerosis. Numerous exudates, hard and discrete, predominantly in left fundus; a few punctate hæmorrhages. No papillœdema.

C.V.S.: Accentuated 1st sound at apex. B.P. 260/140. Pulses present in limbs.

C.N.S.: Coarse lateral nystagmus. Dysarthria. Spasticity of L. arm and leg, active jerks. Plantars extensor.

Abdomen: Spleen, liver, kidneys not palpable.

FIG. 1.—Pigmented macules, moles and fibromata.

Investigations.—X-rays: marked generalized osteoporosis of all bones. Skull: hyperostosis frontalis interna. Spine: early osteo-arthritic changes. Right clavicle: old malunited fracture. Iliac bones: non-union of crests in both bones. Right radius and ulna: old healed fracture deformity at lower end, fairly large simple cyst at lower end of right ulna. Tibia: large hyperostoses medial aspects upper end. I.V.P.: poor contrast, probably normal; no stones.

Blood examination—Urea 35, cholesterol 286, potassium 16·6, sodium 311, calcium 10·3, phosphorus 5 mg.%. Alkaline phosphatase 16·5 K.A. units, Hb 118%, W.B.C. 10,300. Normal film. 17-ketosteroids 0·9 and 1·8 mg./24 hours.

Robinson, Power and Kepler test: Procedures I and II both indicate absence of adrenal insufficiency.

Thorn test: Eosinophil counts before and after ACTH (25 mg.). Before: 107; four hours after: 14.

Glucose tolerance curve: Fasting blood sugar 67 mg.%. Blood sugar at half-hourly intervals after 100 grammes glucose: 97, 161 mg.% and at two and a half hours 132 mg.%.

Insulin sensitivity test (4·5 units): Interval readings over two hours: 61, 39, 50, 54, 42, 50, 59 mg.%.

Urinary gonadotrophins not detected.

Urea clearance test normal. Urine: No albumin or casts. Fat analysis of dried fæces: Total fat 60 grammes per 100 grammes. Split fat 48 grammes; unsplit fat 12 grammes, i.e. of fæcal fat 80% is split, 20% unsplit. W.R. and Kahn negative.

Fractional test meal: Normal acid curve. Benzodioxane test: Slight rise in blood pressure. ECG: Marked left ventricular hypertrophy. Biopsies from arm and scalp: Benign pigmented melanomata.

Comments.—The normal renal findings exclude renal rickets, and the normal blood chemistry makes hyperparathyroidism unlikely.

Idiopathic steatorrhœa does not explain the hypertension and skin manifestations, and the normal glucose absorption curve, hæmoglobin, and serum calcium suggest that the steatorrhœa is not causative.

Neurofibromatosis.—The skin lesions here are very suggestive, but no actual neurofibromata are palpable; and the hypertension, as judged by the benzodioxane test and the absence of a high fasting blood sugar, is probably not due to phæochromocytomata which occur in neurofibromatosis.

Ovarian agenesis.—Her stature, which is short, rather than dwarfed; the body hair, which is reduced rather than absent; the normal hypoglycæmic responsiveness; the associated abnormalities, and especially hypertension, are all more suggestive of primary ovarian agenesis than pituitary dysfunction. But no gonadotrophins can be detected in the urine.

Probably there is no single ætiology for all the abnormalities, which may be due to embryonic maldevelopment affecting various systems.

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Dr. Raymond Greene: My personal preference is for the suggestion in the discussion that the primary disease in this case is steatorrhœa and that the hypertension is coincidental. I can support Dr. de Mowbray's assertion that steatorrhœa can cause both dwarfism and sexual infantilism. I showed a case to this Section in 1949 (*Proc. R. Soc. Med.*, **43**, 359) of a female patient about 4 ft. 6 in. in height with a complete absence of sexual development. She also had a macrocytic anæmia. Her stools did not contain an excess of fat on ordinary single analysis of the dried fæces. The fat balance experiment showed that latent steatorrhœa was present.

Recrudescence of Tuberculosis in Acute Disseminated Lupus Erythematosus Treated with ACTH and Cortisone (Specimen).—F. T. G. PRUNTY, F.R.C.P.

A woman, aged 42, with eighteen months' history of chronic discoid lupus erythematosus was treated with ACTH one month after dissemination, at which time she was critically ill. Before treatment for 37 days with doses varying between 50 and 160 mg. per day (in four divided doses I.M.) there was X-ray evidence of an old healed tuberculous lesion at the apex of the right lung and calcified mesenteric glands.

She subsequently received cortisone by injection and orally for 88 days in doses of up to 100 mg. per day. Finally she received 16 days' treatment with cortisone orally, with doses of up to 150 mg. per day (in three doses). This produced greatly increased albuminuria, œdema, and elevation of blood pressure to 190/110. 33 days later she died in renal failure.

Summary of events.—Days: 1–38, ACTH; 96–184, Cortisone; 250–266, Cortisone; Day 299, Died.

The specimen presented showed spreading tuberculosis involving the upper lobe of the right lung and mediastinal glands. There were also active tuberculous inflammatory lesions in the mesenteric lymph glands. It is a matter for conjecture concerning the relative parts played by the underlying systemic disease and the hormone therapy in the exacerbation of these lesions.

Mixed Type of Cushing's Syndrome and Adrenogenital Syndrome due to Adrenal Cortical Carcinoma: Recurrence.—A. W. SPENCE, M.D., F.R.C.P. (Previously shown at a meeting of this Section on November 22, 1950. *Proc. R. Soc. Med.*, 1951, **44**, 161.)

The patient, a married woman now aged 49, was admitted to hospital two years ago with plethoric facies, generalized obesity; weight 12 st. 12 lb. (81·8 kg.), generalized hirsuties, amenorrhœa, hypertension (B.P. 240/130) and diabetes (typical diabetic type of glucose tolerance curve). Purpuric striæ were absent. Urinary 17-ketosteroids, 42·5 mg./24 hours: urinary 20-ketosteroids, 1·3 mg./24 hours. Dehydro*iso*androsterone could not be isolated. X-ray examination after perirenal insufflation revealed a circular shadow in the region of the right adrenal gland. A carcinoma of the right adrenal gland was removed (13.12.49). Five days later the urinary 17-ketosteroids had fallen to 6 mg./24 hours; one month later plethora less, hair on the limbs was being shed and she had lost 21 lb. (9·5 kg.) in weight. The following month she started to have regular periods. Ten months after operation (26.10.50) hirsuties on limbs and body much reduced, hair on face practically unchanged; B.P. 180/85; she had gained 18 lb. (8·2 kg.) in weight; 17-ketosteroids, 5 mg./24 hours; still diabetic type of glucose tolerance curve.

Subsequent follow-up.—2.3.51: Abdominal hair increasing; weight rising; B.P. 200/100; urinary 17-ketosteroids, 13 mg./24 hours.

1.6.51: 17-ketosteroids, 21·6 mg./24 hours. 3.8.51: 17-ketosteroids, 39·5 mg./24 hours.

26.9.51: Readmitted. Weight 14 st. 10 oz. (89·4 kg.) plethora marked; facial and bodily hair increased; no purpuric striæ; B.P. 240/120; 17-ketosteroids, 63 mg./24 hours; 20-ketosteroids,

4·9 mg./24 hours (upper limit of normal 3·0 mg./24 hours). Glucose tolerance test: fasting blood sugar 100 mg.%, blood sugar at half-hourly intervals after 50 g. glucose: 140, 165, 165, 135 mg.% (improved tolerance). Deep X-ray therapy instituted to right adrenal region, but in spite of this the 17-ketosteroid excretion rose to 109 mg./24 hours during a period of ten days (*see* Fig. 1).

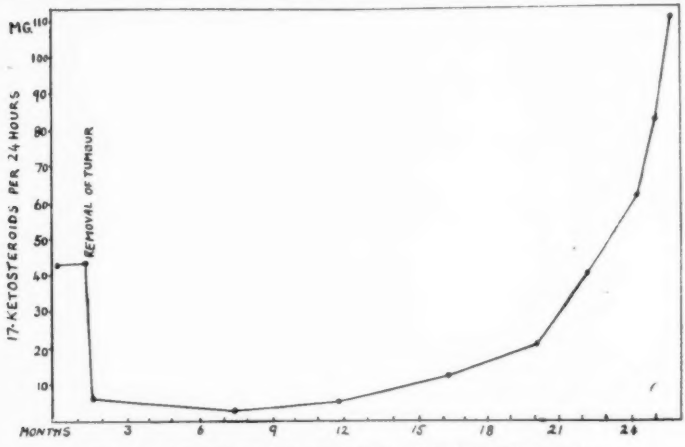

FIG. 1.—Adrenal cortical carcinoma: 17-ketosteroid excretion.

Laparotomy performed and malignant growths found at the upper pole of the right kidney, medially alongside the inferior vena cava and below the diaphragm alongside the aorta. The patient died three days later.

Cushing's Syndrome Associated with Stunting of Growth.—A. W. SPENCE, M.D., F.R.C.P.

Female, aged 26, unmarried. Menarche at the age of 13. At the age of 14 her periods which had occurred at regular monthly intervals became less frequent, occurring every three or four months, she began to gain in weight and the face began to become florid. When aged 24 ulcers developed on both shins—some related to minor trauma—and have not healed since.

On examination.—Height 4 ft. 9½ in., weight 11 st. 3 lb. (71·6 kg.) plethoric facies; obesity mainly of the face, neck and trunk; cutis marmorata on abdomen and thighs; purpuric striæ on abdomen; slight facial hirsuties; B.P. 185/130; deep ulcers on both lower shins. Pelvic examination normal. Urine: no albumin, no sugar. Deposit: occasional red blood cells and white blood cells and a single granular cast.

Investigations.—Blood count: R.B.C. 5,580,000, Hb 110%, W.B.C. 14,000 (eosinophils 5%, i.e. 700 per c.mm.).

Glucose tolerance test: fasting blood sugar, 113 mg.%; blood sugar at half-hourly intervals after 50 gramme glucose, 178, 194, 178, 178; no glycosuria.

Urinary 17-ketosteroids; 15·1 mg./24 hours. Urinary 20-ketosteroids: 4·2 mg./24 hours.

Serum sodium: 325 mg. per 100 c.c. Serum potassium: 16·8 mg. per 100 c.c.

Radiological examinations of: Adrenal regions after perirenal insufflation of oxygen: no evidence of adrenal enlargement. Pituitary fossa: normal in size; osteoporosis. Spine: Osteoporosis with slight wedge-shaping of D 12. Epiphyses: Lower radial and ulnar epiphyses, lower tibial and fibular epiphyses and the left olecranon epiphysis not completely fused. All the epiphyses in the region of the hip-joints fused. Chest: No thymic enlargement; several pathological fractures of ribs.

Treated by radiotherapy to the pituitary gland. Three months later, no change in condition. In an attempt to stimulate protein anabolism and the healing of the ulcers on the legs, she was treated with intramuscular injections of methylandrostenediol, 75 mg. daily for seven days, then 100 mg. twice weekly. After a total dose of 650 mg. the patient developed a papular urticarial rash on the arms, the condition of the ulcers was unchanged and the injections were discontinued.

Comment.—The disorder appears to have begun at the age of 14. It is suggested that the stunting of growth is probably due to the anti-growth effect of excess of cortisone-like substances (e.g. Kendall's Compound F) secreted by the adrenal cortex.

[*January* 23, 1952]

The Pathogenesis of Simple Goitre.—PRESIDENT'S ADDRESS by A. W. SPENCE, M.D., F.R.C.P.

This paper is to be published elsewhere.

Section of Dermatology

President—G. B. DOWLING, M.D., F.R.C.P.

[*December* 20, 1951]

Kaposi's Multiple Idiopathic Sarcoma.—H. C. SEMON, M.D.

The patient, aged 60, a wigmaker by profession, first consulted me on 24.7.51 for an eruption involving both hands. It began insidiously about fifteen months ago round the nailfold of the left little finger and he is positive that this was the initial lesion. There has been a gradual and intermittent spread to the palms, interdigital folds and the left thumb, and there is also a small nodule below and behind the right ear. Latterly a similar but more dusky type of eruption has appeared over the right instep.

Clinically the lesions consist of scattered epidermo-dermal infiltrations of a striking purple or bluish colour. They are elastic and smooth to palpation and are freely movable over the underlying fascia. There are no subjective symptoms beyond a feeling of tension (dead fingers) presumably due to pressure on nerves.

A small gland can be palpated in the right axilla. The liver and spleen are not enlarged.

Radiographs of the chest for hilum deposits, and of the fingers for osteoporosis, were negative, as also were the W.R. and Mantoux tests.

A differential white cell count (27.11.51) revealed a polymorphonuclear preponderance of 84%, lymphocytes 14% and transitional cells 2%. Total W.B.C. 12,600.

Report on sections (Dr. W. Freudenthal): "There is a fairly dense infiltrate throughout the cutis; its special feature is a marked tendency to form new capillaries. *Hæmosiderin is present.* The histological appearances in combination with the clinical picture strongly suggest Kaposi's sarcoma as the diagnosis."

There appears in Kren's excellent symposium in Jadassohn's Handbuch, Vol. XII/3, pp. 911, 912, at least one coloured illustration almost identical both in location and colour with the case presented. The lesions are definitely radio-sensitive and a few have flattened down, leaving brownish stains.

I have been unable to find any reference to the effects of cortisone or ACTH in this disease, but as it is regarded by many authorities as a reticulo-endotheliosis, and experimental investigation on rabbits ("Action of cortisone on mesenchymal tissues", C. M. Plotz *et al.*, 1950, *Arch. Derm. Syph., Chicago*, **61**, 919) has suggested that the hormone has a "profoundly *inhibitory effect* on the development of granulation tissue," its administration would seem to be well worth trying in a disease with frequent visceral complications and an ultra-serious prognosis.

Dr. F. Parkes Weber: We have seen only very few of these cases of Kaposi's hæmorrhagic sarcoma for a long time, but formerly a considerable number were shown, particularly in the time of Pringle and Radcliffe Crocker. I should like to know the general opinion regarding the classification of this disease. In spite of its relatively late onset it seems to belong to the group to which most of the blood capillary dysplasias and hæmangiomatous conditions belong (all of mesenchymatous origin), including the various types of plexiform angiomata in various parts of the body; the vascular features of the so-called Sturge-Kalischer-Weber syndrome, and of course sclerosing angiomata (Dawson, E. K., 1948, *Edinb. med. J.*, 55, 655).

From another point of view (cf. F. P. Weber, 1951, *Brit. med. J.*, ii, 992) I would include Kaposi's hæmorrhagic sarcoma as a nævoid disease.

Dr. J. Sommerville: Regarding cortisone, one of my staff has just returned from the United States and he reports that in treatment of reticulosis, whilst there is initial benefit with cortisone, after it is withdrawn the condition is rather inclined "to go wild", so that in a comparatively mild condition one would hesitate to use cortisone.

Scleroderma with Calcinosis.—H. A. TREBLE, M.R.C.P.

I originally saw this housewife, aged 39, eleven years ago with an area on the outer side of the right thigh 15 cm. in diameter, which was erythematous, depressed below the surface and deeply attached to muscles. Very shortly afterwards, she developed typical dermatomyositis of the face. Gradually during the next two years scleroderma appeared in the fingers and toes with increasing stiffness of the limbs and also a wide area of scleroderma with telangiectasia on the shoulders, upper chest and back. Around the shoulders and along the flexor tendons of the forearm and palms, hard, calcified, nodular lesions developed, some of which have ulcerated to discharge calcareous spicules. She has also developed some nodular sclerodermatous lesions around the hips which later calcified. On the whole the lesions of the face have improved in recent years.

She has complained of some dysphagia. X-rays reveal no abnormality of the pharynx or œsophagus, and the condition appears to be due to stiffness of the neck tissues as a whole. A barium meal revealed no intestinal lesions. The heart is of normal size and shape on X-ray.

Hæmoglobin 98%. C.I. 1·0; white cells 5,800; differential normal. Serum calcium 10·9 mg.%; blood phosphorus 3·1 mg.%; serum acid phosphatase 2 units (Gutman) per 100 ml.; serum alkaline phosphatase 5·8 units (K.A.) per 100 ml. Wassermann and Kahn tests negative.

In the early stage she was treated for some weeks with 40 grammes glycine daily with no apparent benefit. Attempts at treatment with calciferol 25,000 units daily eighteen months ago had to be abandoned owing to nausea and vomiting.

The President: Is there any great degree of skeletal and muscle weakness?

Dr. Treble: She said she had great difficulty in walking because of stiffness rather than weakness.

The President: She seemed to have lost a great deal of muscle, and there was a good deal of wasting. The case seems to be a perfect example of the half-way house between dermatomyositis and progressive symmetrical scleroderma.

Liquefying Nodular Panniculitis.—B. SCHWARTZ, M.D.

Mrs. K. C., aged 41, developed an ulcer behind the right knee in August 1950, which she attributed to an infected mosquito bite. The ulcer was described as unusual and did not heal until April 1951. There was no constitutional disturbance.

In May 1951 she was admitted with acute abdominal pain in the right hypochondrium and right iliac fossa. ? cholecystitis. Temp. 102·2° F. E.S.R. 41 mm. in one hour (Wintrobe). Other investigations normal.

The pyrexia continued and after one week she developed a small right pleural effusion from which 130 c.c. of a yellow serous fluid was aspirated. Culture was sterile, no tubercle bacilli seen. In three weeks the pyrexia subsided under treatment with streptomycin, and the pleural effusion cleared.

From October 1951 diarrhœa occurred on and off for two months and right-sided abdominal pain for three weeks. A tender mass was felt toright of umbilicus, and she was readmitted. ? Crohn's disease.

Six tender red fluctuant swellings about 3 cm. in diameter were then seen on the legs. These had appeared within four to five days and were breaking down. She reported that for three weeks her temperature had risen from 99° F. in the morning to 103° F. at night.

FIG. 1.—Liquefying nodular panniculitis, showing ulcerated lesions on thigh.

An intermittent fever continued and new tender areas developed on the limbs, beginning as firm masses 1–4 cm. in diameter, which softened, broke down and discharged a yellowish-brown serous fluid and left an undermined crateriform ulcer (Fig. 1). The course from appearance to breakdown was ten to fourteen days.

Treatment with chloramphenicol 0·5 gramme six-hourly was commenced on 22.11.51. This caused a rapid decline of the fever and although new tender areas appeared there was a distinct slowing in their evolution. The ulcers began to heal, the mass in the right iliac fossa disappeared, but a new mass was palpable in the left hypochondrium.

Present condition.—Is still an inpatient at St. George's Hospital under Dr. C. B. Levick. She is afebrile and has lost about 1 stone (6·4 kg.) in weight since October 1951.

There is one unruptured but fluctuant mass over the left deltoid. Unhealed undermined ulcerations still discharging yellowish fluid are present on the anterior aspects of the thighs, and depressed atrophic pigmented scars at the sites of previous ulcerations. There is no abdominal tenderness. The spleen is not palpable. There is no abnormal glandular enlargement.

She gives no history of having taken iodide or bromide medicines. There is nothing significant in her past medical or family history.

Investigations.—Repeated and careful examination of fluid from the abscesses showed no tubercle bacilli or other organisms and culture was sterile.

Blood count normal. E.S.R. (Wintrobe) 25 mm. in one hour. Blood urea 16 mg.%. W.R. and Kahn negative. Serum proteins: Total 7 grammes %. Albumin 1·7. Globulin 5·3. A.G. ratio 0·3 : 1. Serum amylase normal. Urine showed no abnormality: Culture negative. Diastase index = 6. Stools normal, no pathogens on culture. Fæcal fat: Total 36·9 grammes; 67% split, 33% unsplit.

X-rays.—*Chest*: Small area of pleural thickening on right side. *Opaque meal*: No radiographic evidence of organic lesion in œsophagus, stomach or duodenum. No obstructive lesion in large intestine. *Opaque enema*: No intrinsic abnormality detected in colon.

Biopsy.—An unruptured lesion from right thigh was removed.

Pathological report (Dr. N. F. C. Gowing): A portion of subcutaneous adipose tissue. Microscopically shows a cavity in the adipose tissue which is filled with debris and some inflammatory cells. Inflammatory cell infiltration can also be seen in the connective septæ of the surrounding fat. Focal collections of foam cells and multinuclear giant cells are also present. No bacteria can be found.

Comment.—This patient has, over the past eighteen months, presented the clinical picture of recurrent febrile attacks, a pleural effusion, abdominal pain with the formation of tender masses in the abdomen, and the appearance of tender areas on the limbs. Over a course of ten to fourteen days these areas softened, broke down and discharged a yellowish-brown fluid and left an undermined ulcer. Some of the areas later healed leaving depressed pigmented scars.

Histologically the lesions show a fat necrosis and this, with the blood and bacteriological investigations, excluded the possibility of erythema nodosum, erythema induratum, sarcoidosis and syphilitic or tuberculous ulcers. No fungi were seen on examination and there was nothing to support a diagnosis of periarteritis nodosa or nodular vasculitis. In lipomatosis the fatty tumours do not break down, nor is there any systemic reaction.

Three other possibilities were considered:

Firstly, that the skin lesions were secondary to an abdominal neoplasm.

An attractive theory was the presence of a pancreatic tumour with lipolytic secondaries, but there appears to be no pancreatic disturbance and the healing of some lesions makes this unlikely.

Secondly, the possibility of artefact.

Although artefact lesions would not explain the constitutional disturbance or, for example, the serum-protein changes, steps were taken to exclude the possibilities of the patient producing the lesions herself.

Lastly, Weber-Christian disease.

The classical picture of relapsing febrile nodular non-suppurative panniculitis is now well known. Histologically this shows a fat necrosis, the presence of some cellular infiltration, macrophages, foam cells and foreign body giant cells, which is the histology in this case.

Although excluded by the definition, liquefaction of Weber-Christian nodules has been reported twice before. In 1938 Shaffer used the term "Liquefying Nodular Panniculitis" to describe the case of a woman of 33 who had had recurrent abscesses for ten years. These began as woody, tender masses the size of a walnut or an egg, which ruptured and discharged an oily, yellowish-brown fluid. This occurred over a febrile course of ten to fourteen days. It was this report which probably prompted Ormsby and Montgomery to include the possibility of liquefaction in their textbook description of the disease (1948). Binkley, in 1939, also reported liquefaction of a Weber-Christian lesion. More recently Bunnell and Levy (1948) described lesions which were occasionally fluctuant.

It is always satisfying if a single diagnosis can be made to cover the multitude of a patient's symptoms, and it is suggested that Weber-Christian disease or its variant, liquefying nodular panniculitis, will do so in this case. The skin lesions have, I think, been accounted for. In a fatal case reported in 1944 Spain and Foley described necrotic nodules in the mesenteric and omental fat. The presence of such nodules here would explain the abdominal pain and the masses felt at different times in different areas of the abdomen.

Miller and Kritzler (1943) have described fat emboli in the lungs, and Hartwell and Thannhauser (1940) also report a pleural effusion in Weber-Christian disease. There may be a similar occurrence here.

A variety of different treatments have been used in Weber-Christian disease. It is always difficult to assess the value of treatment in relapsing diseases, but many drugs are reported to produce remissions. It was to be expected that cortisone would be used and in a recent case in America this reduced the fever but the case subsequently ended fatally (Shuman, 1951).

Chloramphenicol was used empirically in the present case and we have been most impressed with its effect. There has been no recurrence of the fever since its use was discontinued a few days ago.

(I am indebted to Drs. C. B. Levick and M. I. A. Hunter for their permission to show this case.)

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Dr. F. Parkes Weber: I think the suggested diagnosis is quite possible, and I think that one or two cases have been observed in which the nodules have broken down as in this case, but I have not seen any myself.

The following cases were also shown:

Lymphocytoma Cutis.—Squadron Leader L. H. TRUELOVE for Dr. ALICE CARLETON.

Miliary Lymphocytoma of Scalp and Face.—Dr. H. A. TREBLE.

Keratoderma Disseminatum Palmaris et Plantaris.—Dr. ARTHUR PORTER.

(1) **Mycosis Fungoides.** (2) **Scurvy.**—Dr. D. L. REES (introduced by Dr. G. B. DOWLING).

Extensive Hairy Nævus of Face, Treated by Belly-arm Flap Replacement with Post-auricular Grafts to the Eyelids.—Mr. PATRICK CLARKSON.

Acute Disseminated Lupus Erythematosus Treated with ACTH.—Dr. C. H. WHITTLE.

Lichen Sclerosus et Atrophicus.—Dr. A. LYELL.

Melanosis.—Dr. D. I. WILLIAMS.

Multiple Self-healing Epitheliomata (Ferguson-Smith).—Dr. P. D. SAMMAN.

(These cases may be published later in the *British Journal of Dermatology*.)

[*January* 17, 1952]

Poikiloderma Vasculare Atrophicans (with Reticulosis).—STEPHEN GOLD, M.D., M.R.C.P.

J. B., aged 30, was first seen in November 1950, having been referred from the Ministry of Pensions. Eleven years ago, when he was serving in the Army, he noted a scaly pink patch on his left upper arm which was sore but never irritated; later, other patches developed on the lower abdomen, right upper arm, outer side of right thigh and, more recently, under his right axilla, on the left buttock and smaller ones scattered on the trunk (Fig. 1). A biopsy was performed while he was in the Army and the report apparently was that of a tuberculide. Later he was seen at Cardiff and a diagnosis of parakeratosis variegata was made. He was subsequently invalided from the Army and was referred to West London Hospital where parapsoriasis was diagnosed.

FIG. 1.—Atrophic pigmented areas scattered over body.

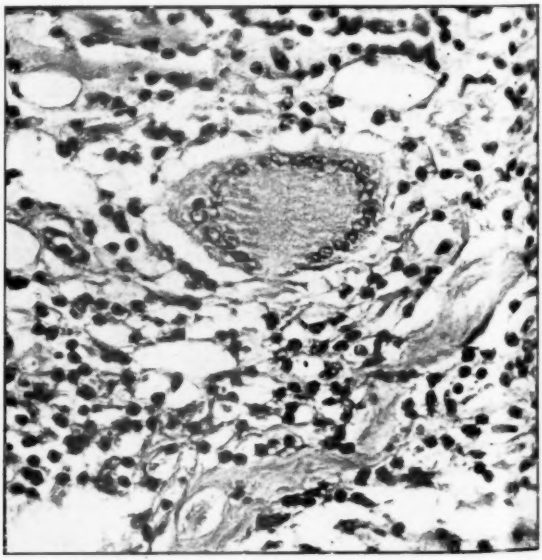

FIG. 2.—Histological section from axillary tumour, × 335, showing presence of typical Langhans' giant cells amidst pleomorphic infiltrate.

On examination in 1950, he revealed multiple areas resembling chronic radio-dermatitis; these were pigmented and atrophic, the skin resembling tissue paper. Some show moderate scaling and feel slightly infiltrated, while hæmorrhagic puncta and dilated vessels are visible but true lichenoid papules are absent.

There was no lymphadenopathy or enlargement of spleen or liver.

White blood count total 4,700 cells per c.mm. Differential count normal. No eosinophilia.

The diagnosis of poikiloderma of the Lane type was made and a biopsy performed.

Histological report (November 1950).—Epidermis is atrophic but granular layer is intact. The basal layer shows hydropic changes and there is marked flattening of the dermo-epidermal junction. In the subpapillary region there is a dense infiltrate composed largely of lymphocytes and histiocytes; occasional plasma cells and polymorphs are present and numerous melanophages. This infiltrate encroaches the epidermis in places to form so-called "Pautrier's abscesses". The infiltrate extends into the subcutaneous tissue but certainly at this depth it is less dense. Giant cells are not apparent.

The only symptom of which he complained was of dryness and soreness of the skin, which would readily crack during the cold weather, particularly under the right axilla where a small fissure developed into a chronic ulcer; this would heal and break down again. The local application of thorium X did not produce any marked change, neither did a course of systemic penicillin (9,000,000 units over fourteen days).

He has been seen regularly as an out-patient and his general health is unimpaired. He complains of no symptoms apart from the dryness and soreness and is working as a street trader. He has gained weight recently (1 stone (6·4 kg.) in six months).

In November 1951 a mass was detected in the right axilla lying underneath an area of poikilodermatous skin and apparently in the substance of the latissimus dorsi muscle, but a biopsy showed the subcutaneous tissue to be œdematous and the mass to be lying on the surface rather than in the muscle.

Histological report (January 1952).—The tissue is composed of a dense cellular infiltrate the majority of cells being lymphocytes and histiocytes with occasional polymorphs and plasma cells. Necrosis is absent and there is no apparent follicular arrangement, although this is revealed with reticulin stains. There are no giant cells typical of mycosis fungoides or of Reed-Sternberg cells. There are, however, fairly numerous and perfect examples of Langhans' giant cells (Fig. 2).

Comment.—This case resembles identically the one reported by Oliver (1936) in which similar cutaneous changes were present in a patient suffering from mycosis fungoides. Ulceration is an unusual feature and occurred in Lane's original case (1921), who eventually died of Hodgkin's disease. It is also interesting that the patient reported by Ormsby (1917), who died of lymphosarcoma, was an obese young man like my patient. I hesitated to make a diagnosis of mycosis fungoides because of the presence of typical Langhans' giant cells in the tissue removed from the axillary tumour, though in other features the cellular infiltrate is quite typical.

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Poikiloderma Vasculare Atrophicans with Early Mycosis Fungoides.—R. G. HOWELL, B.M., M.R.C.P. (introduced by G. B. DOWLING, M.D., F.R.C.P.).

Mrs. R. R., a widow aged 65.

History.—Five years ago she developed a non-irritant rash on the arms and legs, which remained unchanged until eight months ago when there was spread to the trunk and slightly to the face. At that time scattered plaques and papules, which irritated, appeared on the trunk and limbs.

Previous history.—Nothing relevant to the present complaint.

On examination.—There are diffuse areas of poikiloderma on the limbs and trunk, with slight scaling of the palms and soles and on the face. Scattered in the areas of poikiloderma on the trunk and limbs are numerous red infiltrated plaques and papules. The mucosæ are normal except for two small erythematous patches on the palate. The appearance of the lesions on the trunk has been altered by recent treatment with Grenz rays (3 applications of 1,000 r at weekly intervals). There is no lymphadenopathy and the spleen is not palpable. There is no muscle weakness. General examination shows no other abnormality.

Histology of a papule from the chest (Dr. I. W. Whimster).—"There is moderately severe epidermal atrophy, with diffuse infiltration of the upper dermis by inflammatory cells of many types, including some atypical forms."

Comment.—This case is another example of mycosis fungoides supervening after a long latent period on the poikiloderma of Jacobi and Lane.

Poikiloderma Vasculare Atrophicans of Jacobi-Lane.—J. B. LYON, M.B., M.R.C.P. (for J. L. FRANKLIN, M.D., M.R.C.P.).

Male, aged 30. Engineer.

He first noticed scaly red patches on the extensor aspect of the elbows about ten years ago; there has been a gradual progression over the years to involve most of the body, the trunk being relatively spared. During the past three years the ears and eyelids have become red and scaly but not swollen. His general health has otherwise been good, without any relevant family history.

There was extensive and widespread erythema with telangiectasia on both arms, buttocks and legs. Areas of pigmentation were present behind the knees, and on the right thigh there was a well-marked linear arrangement of the pigment with some reticulation. Pinkish lichenoid papules (as described by Gougerot and Eliascheff) could be seen in the more markedly erythematous areas.

An extensive area of erythema with a centre simulating X-ray dermatitis and early atrophy was present on the left buttock. On the whole, there was not a great deal of atrophy so far. Both hands were dry and a dusky bluish-red colour. The trunk was relatively spared except for a fine generalized scaling; the ears and eyelids showed a scaling erythema without œdema, the skin over the former being rather stretched out and tight. His general condition was good and all other systems were normal.

A biopsy was taken from the extensor surface of the arm and above the elbow; the sections showed epidermal atrophy which was discontinuous and loss of basal cells and rete pegs in the affected patches. The superficial layers of the corium showed areas of round-cell infiltration, and at this level there was some loss of elastic tissue.

Comment.—This case seemed to fit in with the more classical type of poikiloderma (Jacobi-Lane).

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Dr. H. Haber, referring to Dr. Gold's case: The presence of Langhans' cells does not militate against a diagnosis of reticulosis. I have seen a case of lymphocytic reticulosis exhibiting many Langhans' cells. Later on the case became clinically and histologically mycosis fungoides. I regard the Langhans' cells as reactive cells due to the metabolic products of the neoplasma and not as tumour cells.

Dr. D. I. Williams: I think one can divide these cases into two groups. There is the type which we have seen to-day with curiously defined and localized skin changes, the patient's skin otherwise seeming to be quite normal; this type seems to go on to one or other of the reticuloses. Then there is the other type found more often in patients who come from the countries of Central Europe, in which the eruption is usually universal and there seems to be much more pigmentation. I do not think this second type ever goes on to a reticulosis, but perhaps I have not been able to follow such cases for a long enough time.

Dr. L. Forman: I agree that Dr. Lyon's case has better claim to the title of poikiloderma than the other 2 cases shown by Dr. Gold and Dr. Howell. I had a similar patient, a male, in whom the redness and atrophy involved a larger part of the body. I have had him under observation for twelve years and there has been no evidence of reticulosis. One does get the impression that this inflammatory reaction has completely died out and that it would be unlikely that a reticulosis would develop.

Dr. E. Waddington: A patient I showed here a year ago (*Proc. R. Soc. Med.*, 1951, **44**, 673) had widespread lesions which had been present for twenty-five years, before any infiltration occurred. Oliver (1936, *Arch. Derm. Syph. Chicago*, **33**, 267) in a review of the subject described a number of cases in which mycosis fungoides appeared twenty years after the onset of poikiloderma. My case was originally presented to the Section by Dr. G. Mitchell-Heggs and Dr. F. W. Jacobsohn (*Proc. R. Soc. Med.*, 1936, **29**, 717) as a case of poikilodermia, and the biopsy showed the presence of the typical lichenoid papules seen in this condition.

Dr. Gold: My impression was that the lesions in my patient were identical with those of the main type.

The President: There is a certain family resemblance between the cases.

The following cases were also shown:

Dermatofibrosarcoma.—Dr. F. RAY BETTLEY.

Multiple and Nævoid Rodent Ulcers of Face (Paul).—Dr. O. L. S. SCOTT.

Two Cases of Ringworm.—Dr. C. D. CALNAN.

Tuberculide or Sarcoid.—Dr. D. L. REES for Dr. G. B. DOWLING.

(These cases may be published later in the *British Journal of Dermatology*.)

Proceedings of the Royal Society of Medicine Vol. 45 179

Section of Anæsthetics

President—JOHN GILLIES, C.V.O., M.C., M.R.C.P.Ed., F.R.C.S.Ed., F.F.A. R.C.S.

[*December* 7, 1951]

Decamethonium Iodide (C 10): Some Observations on its Action Using Electromyography

By H. C. CHURCHILL-DAVIDSON, M.B., D.A., and A. T. RICHARDSON, M.B., D.Phys. Med.
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THE isolation by King in 1934 of the active principle from curare initiated the use of muscle relaxants in anæsthesia. Since that time there have been many attempts to prepare synthetic muscle relaxants, including the preparation and study of the methonium compounds. Of the methonium series, decamethonium salts showed sufficient promise to be tested in man and finally became established as a useful muscle relaxant for use in surgical anæsthesia and convulsion therapy.

This paper will deal with the changes in form and amount of the electrical activity of intact human voluntary muscles which occur when decamethonium iodide (C 10) is given intravenously. Particular reference will be made to the effect of blood flow on the duration of action of this drug and the remarkable tolerance of patients suffering from myasthenia gravis to its action.

ACTION OF DECAMETHONIUM IODIDE

It has been established by Paton and Zaimis (1949), Buttle and Zaimis (1949), Zaimis (1951), Brown, Paton and Vianna Das (1949) and more recently by Burns and Paton (1951) that decamethonium salts produce muscle relaxation in a way fundamentally different from that of curare and in fact have an action similar to that of acetylcholine. Dale, Feldberg and Vogt (1936) showed that the stimulus of contraction from motor nerve to voluntary muscle takes place by the release of acetylcholine at the nerve endings. The function of this acetylcholine is to excite the motor end-plate and initiate muscle contraction. This excitation is short-lived, because acetylcholine is rapidly destroyed by cholinesterases in the muscle, but it can be identified by the simultaneous electrical changes which give rise to the action potential associated with muscle contraction. The electrical changes accompanying excitation are referred to as depolarization. Similar changes are produced by decamethonium iodide, but since this substance is not rapidly destroyed, they are prolonged. Thus, following the initial brief muscle contraction accompanying depolarization, the muscle fibre is unable to respond to further nerve impulses until it regains its original state. In fact, a condition of neuromuscular block is produced. All this is in contrast to curare which raises the threshold of the motor end-plate for acetylcholine, thus preventing depolarization taking place.

METHODS OF ASSESSING THE EFFECTS OF MUSCLE RELAXANTS

(*a*) *Mechanical methods.*—Previous investigations on human subjects with decamethonium iodide have generally been made by mechanical methods alone; the apparatus used being variously referred to as a dynamometer or an ergometer. For the sake of uniformity throughout this paper the term ergometer will be used. Thus Guild (1950) measured grip strength with a mercury column ergometer while Unna *et al.* (1950) used spring ergometers.

(*b*) *Electromyographic methods.*—When muscle fibres contract in response to nerve impulses, the phenomenon of depolarization spreads along the fibre giving rise to a propagated action potential which may be studied by electromyography. In the investigation of neuromuscular diseases electromyography is used in two ways. First, to study the dimensions of single muscle action potentials from which may be determined the site of pathological lesions and second, to measure the total electrical discharge of a muscle which may be used as an index of the number of contracting muscle fibres stimulated in various ways. These quantitative measurements may be used, for instance, to measure neuromuscular transmission in myasthenia gravis and to follow the course of peripheral nerve injuries. They may similarly be used to study the action of muscle relaxants.

Electromyographic techniques have advantages over techniques based on mechanical methods. Apart from the portability of electromyographic equipment which makes it easy to use in the operating theatre, measurements from a single muscle can be readily obtained. Further, whereas measurements of muscle power by ergometers demand a full volitional effort on the part of the subject, a matter of some difficulty when muscle relaxants are administered to myasthenics, with the electromyographic technique a supramaximal electrical stimulus can be supplied to the peripheral nerve. This allows its use even in unconscious subjects. The supramaximal nerve stimulus may, of course, be delivered at various rates and therefore the degree of neuromuscular block with muscle twitch and tetanus may be determined.

The muscle contraction produced by electrical stimulation of a motor nerve is, however, different from that produced by a voluntary contraction. The functional unit of normal muscle is the motor unit which is defined as the ventral horn or motor nerve cell and the group of muscle fibres it supplies. It follows that the discharge of a single motor neurone brings about the almost simultaneous contraction of the hundred or so muscle fibres that are supplied by this neurone. Maximal voluntary contraction invokes the activity of many of these motor units acting asynchronously at an average maximum rate of 20 per second; this graded activity of motor units provides for the smooth contraction of muscle. In contrast, electrical simulation of the nerve produces a synchronous discharge of all the motor units. This difference is, however, irrelevant to comparative measurements of muscle power during the administration of muscle relaxants.

Technique

Electromyographic measurements of hypothenar muscle activity were used to assess the effect of decamethonium iodide on peripheral musculature and a mercury column ergometer used to measure grip strength. To analyse individual muscle action potentials co-axial needle electrodes (S.W.G.24) made of stainless steel with copper cores were used. Following detection the action potentials were amplified by a conventional high gain differential amplifier. The time constant of the amplifier was 0·1 per second and the frequency response was 6 decibels down at 1·6 cycles and 8 kilocycles. After amplification the potentials were recorded on magnetic tape (overall time constant 5 millisecs.). These recordings, which could be selected at will, were then displayed on a cathode-ray tube from which they were photographed.

For measurements of muscle power, supramaximal electrical stimulation of the ulnar nerve was effected at the wrist or elbow, and the total muscle action potential detected with skin electrodes. The skin electrodes were held in position by suction and contact made with electrode jelly. The resultant potential was displayed on a cathode-ray tube, photographed, enlarged, and finally its height measured (Fig. 1). As the height of the potential diminished, due to the paralysing action of decamethonium, so the results were compared with the control value and expressed as a percentage degree of paralysis. Following recovery the action potential was compared with the control, and results were only acceptable if exact matching between the two action potentials was obtained. Thus technical errors due to movement of the skin electrodes were eliminated. Although a stimulation rate of 20 per second is more nearly that of normal motor unit activity, 10 per second was used in this investigation. In this way neuromuscular block due to myasthenia, which rapidly occurs at the rate of 20 per second, was avoided. It can be shown that, in contrast to curare, the rate of nerve stimulation does not alter the degree of neuromuscular block produced by decamethonium iodide in normals (Fig. 2). Stimulation was carried out intermittently at two-minute intervals for 5 seconds. The duration of the electrical stimulus used was 0·3 millisecond and it was rendered earth free by a transformer. Such a short stimulus can only excite muscle via the nerve and cannot directly stimulate the muscle.

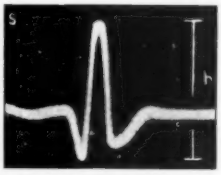

Fig. 1.

Fig. 1.—Action potential of the hypothenar muscles on stimulation of the ulnar nerve. S denotes stimulus artefact.

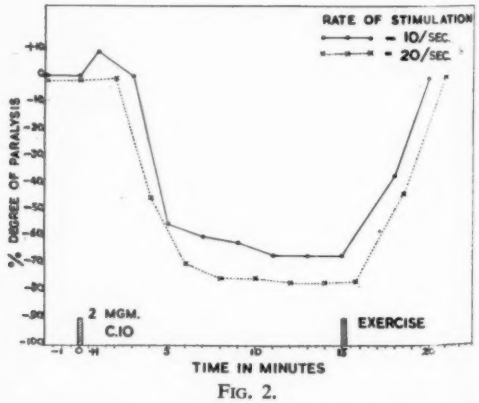

Fig. 2.

Fig. 2.—The effect of the rate of nerve stimulation on the degree of paralysis produced by decamethonium.

In keeping with the results described by Organe (1949), it was soon found that wide variations in the response to decamethonium iodide occurred and it was not possible to relate the dose of decamethonium iodide necessary to produce a constant degree of paralysis to the body-weight of conscious volunteers. A method involving a standard dosage was therefore necessary. Following the measurement of a control action potential each subject was given 1·5 mg. of decamethonium iodide intravenously. After an interval of four minutes, a further measurement was made and if there was less than a 50% reduction in height of the action potential then a further 0·5 mg. was given. This

procedure was repeated at two-minute intervals until approximately a 60–80% reduction in the action potential was produced, or in myasthenics distressing symptoms began to occur. An interval of four minutes was thought to be necessary if the full effect of the first dose was to be manifest before proceeding. Subsequently the intervals were reduced to two minutes so that all the injections were completed within fifteen minutes. This ensured that the initial dose was fully active before the investigation was complete.

Results

(1) *Clinical signs and symptoms.*—(*a*) *Intravenous*: The signs and symptoms following the injection of C 10 into conscious volunteers fell largely into two groups. The first group started 15–20 seconds after the injection and consisted of double vision, ptosis and squint. In some people a feeling of tightness in the jaw and calf muscles was experienced. Dysphagia and dysphonia followed a large dose (such as 3 mg.). These symptoms and signs started to disappear in two or three minutes in the same order as their onset.

The second group usually came on about four minutes after the injection as a rapidly increasing degree of paralysis shown by a reduction in grip strength and a reduction in the height of the muscle action potential. In fact, initially the bulbar musculature was mainly involved whereas the peripheral muscles seemed to be affected some minutes later.

(*b*) *Intra-arterial*: In addition to the technique using divided intravenous doses of decamethonium, some experiments with intra-arterial injections were carried out. It may be of interest to mention the effects of an intra-arterial injection since there does not seem to be any reference to this in the literature. A continuous injection of the brachial artery with a power-driven syringe was used. Two minutes after starting, the infusion at 10 micro-gramme/minute a dull deep ache developed, starting in the region of the needle and spreading rapidly down the arm. This dull feeling, occurring deep in the arm, increased in intensity until it became an unpleasant ache as the paralysis became complete. On stopping the infusion the pain passed off in about two minutes and recovery from the paralysis commenced in ten to twenty minutes. The time taken to return to normal depended largely on whether exercise was undertaken or not (*vide infra*).

(2) *Site of action of decamethonium.*—Electromyographic study showed that the initial depolarizing action of decamethonium iodide was accompanied by a shower of muscle action potentials. This was most readily demonstrated in denervated muscle where the muscle fibres are abnormally excitable (Zaimis, 1951). Reference to Fig. 3 shows that stimulation of the intact motor unit distal to the point of branching of the nerve fibre would be expected to produce single muscle fibre potentials. However, stimulation of the lower motor neurone in this area may excite the entire motor unit. Similarly, if stimulation of the motor unit occurs above the point of branching of the lower motor neurone, it results in the contraction of all the fibres of the motor unit. Excitation of entire motor units results in a shower of whole motor unit potentials, as opposed to single muscle fibre potentials which occur if the muscle fibres are stimulated directly. In fact, muscle activity of apparent motor unit origin does occur with decamethonium iodide and can be seen as fascicular twitching. It is unlikely that these apparent motor unit discharges arise from either summation of individual muscle fibre potentials or from volitional activity. It remains to be determined whether they are due to direct stimulation of the lower motor neurone by decamethonium or to a spinal reflex.

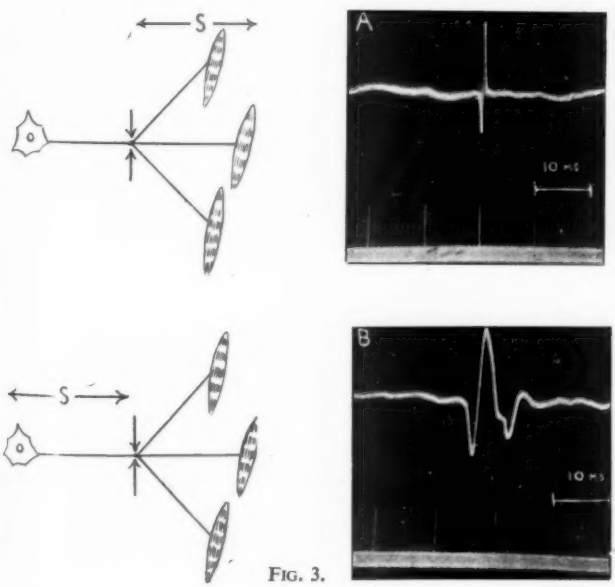

FIG. 3.

FIG. 3.—Electromyographic appearances from stimulation of the motor unit. *Upper*: Stimulation (S) below the point of branching of the lower motor neurone produces a single fibre potential (A) or a motor unit potential. *Lower*: Stimulation (S) above the point of branching of the lower motor neurone produces a motor unit potential (B).

When partial paralysis from neuromuscular block had occurred with decamethonium iodide volitional motor unit potentials became smaller in amplitude and duration than normal. This cha can only be produced by the failure of some of the muscle fibres constituting the motor unit contribute their part of the motor unit potential and indicates a lesion distal to the point of branchi of the lower motor neurone. In contrast, if paralysis occurred above this point it would result inactivity of the entire motor unit (Fig. 4).

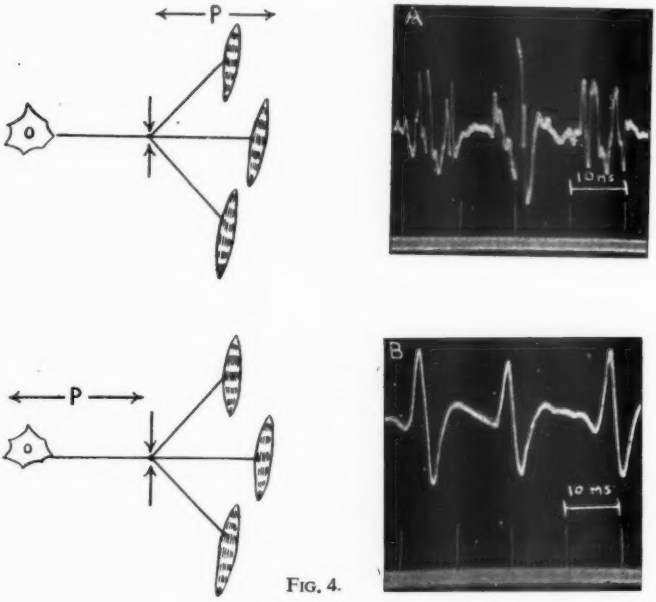

FIG. 4. — Electromyographic appearances from paralysis of the motor unit. *Upper*: Paralysis (P) below the point of branching of the lower motor neurone produces disintegration of the motor units (A). *Lower*: Paralysis (P) above the point of branching of the lower motor neurone reduces the total number of motor unit potentials (B).

Following complete paralysis of voluntary muscle activity by decamethonium iodide, the muscles still respond to direct electrical stimulation. It is thus evident from this finding and the electromyographic changes in innervated and denervated muscles that the site of action of decamethonium is at the neuromuscular junction, as has been shown in the animal experiments that have been described.

(3) *The effect of blood supply on the action of decamethonium iodide.*—It was observed in conscious volunteers that about twenty minutes after the injection of decamethonium iodide, although the ergometer showed that full motor power had returned to the upper limb, the subjects had extreme difficulty in walking. In fact it appeared that although the effects of the drug had worn off in the upper limb, the lower limbs were still partially paralysed. Further, if the subjects exercised their legs for a few minutes a rapid improvement in strength occurred. A study of the effect of exercise on the rate of recovery from paralysis induced by decamethonium iodide was obviously required to clarify these observations. Measurements of muscle power as registered by the electromyograph and ergometer were therefore made of the upper limbs while one limb was kept at rest and the other was exercised. It became evident that the duration of paralysis of muscles following decamethonium administration to conscious subjects at rest was considerably longer than twenty minutes (Fig. 5). In fact, the paralysis did not reach its maximum until about the twentieth minute after the injection, when the arm remained passive (Table I).

It was necessary to determine why exercising a muscle should so alter the duration of paralysis following the injection of decamethonium iodide. Exercising a muscle undoubtedly increases the blood supply through it and this was thought to be a factor of the utmost importance. To investigate this various experiments were carried out:

(*a*) *The effect of variation in temperature*: One limb was heated by an infra-red lamp while the other limb was cooled with ice-bags. Electromyographic measurements were used, because unlike ergometric measurements these allowed the limbs to be almost completely at rest. It was observed that the heated limb showed a rapid onset and recovery of paralysis whereas the cooled limb showed a slow onset of paralysis which reached its maximum and remained at this level until the arm was heated (Fig. 6).

TABLE I.—THE EFFECT OF VARYING DOSES OF DECAMETHONIUM ON 7 CONTROL SUBJECTS SHOWING THE TIME OF ONSET OF PARALYSIS AND TIME OF ATTAINMENT OF MAXIMUM PARALYSIS IN A RESTING LIMB. DEGREE OF PARALYSIS INDICATED IN BRACKETS.

Patient	Single injection of C 10	Time in minutes: Start of paralysis	Time in minutes: Maximum paralysis
A	3·0 mg.	3 min. (62%)	20 min. (84%)
B	3·0 mg.	3 min. (68%)	19 min. (80%)
C	2·5 mg.	4 min. (20%)	25 min. (74%)
D	2·5 mg.	4 min. (12%)	19 min. (80%)
E	2·0 mg.	7 min. (64%)	24 min. (86%)
F	2·0 mg.	4 min. (46%)	19 min. (80%)
G	2·0 mg.	7 min. (18%)	17 min. (50%)
Average	2·5 mg.	4·5 min. (41%)	20·5 min. (76%)

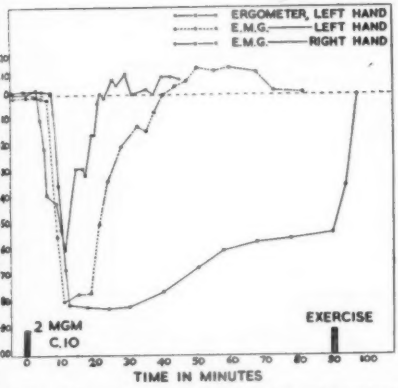

FIG. 5.—Comparison of the duration of paralysis from the administration of 2 mg. of decamethonium in resting limb (right) and exercising limb (left).

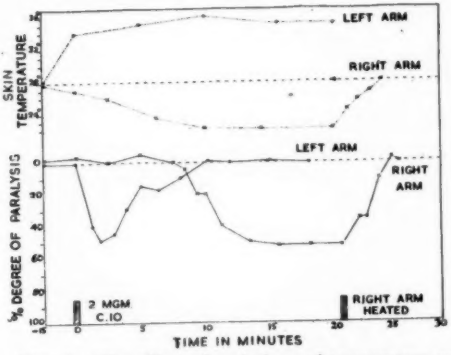

FIG. 6.—The effect of variations of temperature on the duration of paralysis following decamethonium (skin temperature recorded).

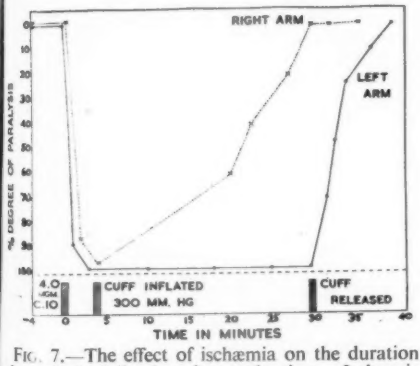

FIG. 7.—The effect of ischæmia on the duration of paralysis following decamethonium. Ischæmic arm (left) compared with control arm (right).

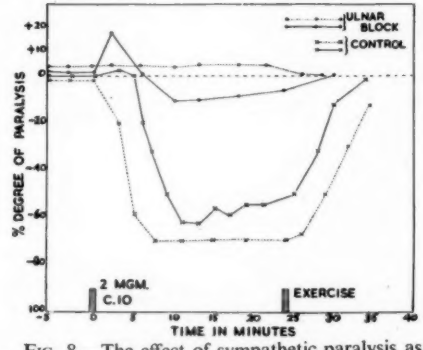

FIG. 8.—The effect of sympathetic paralysis as produced by an ulnar nerve block on the paralysis following decamethonium.

(*b*) *The effect of ischæmia*: In this investigation, one subject was anæsthetized with thiopentone, nitrous oxide and oxygen and an occlusion cuff applied to the arm after paralysis. It was already known that thiopentone in clinical doses did not affect neuromuscular transmission. 4 mg. of decamethonium iodide produced complete paralysis in both arms in three minutes. The control arm showed recovery in normal time but the occluded arm remained paralysed until the cuff was released. On the release of the cuff a marked hyperæmia occurred and the arm recovered 50% of its motor power in three minutes (Fig. 7).

(c) *The effect of sympathetic paralysis*: In three subjects the ulnar nerve was blocked with 10 ml. of 4% procaine at the elbow. Full motor and sensory paralysis was produced in each case, and therefore full sympathetic paralysis must have taken place. An increase in blood supply due to sympathetic paralysis was obtained and confirmed by recordings of the skin temperature. Electromyographic measurements of muscle power showed that following the injection of decamethonium iodide, the control arm had a typical response but the arm with the ulnar block had almost no paralysis (Fig. 8). It was not anticipated that blocking of the ulnar nerve would have such a marked effect on the action of decamethonium iodide. Although increase in the blood flow obviously plays a very important part, it is possible that some other factor, as yet unknown, may also be involved. This effect is unlikely to be due to the presence of procaine in the circulation as it is not produced when a large subcutaneous depot of procaine is placed in the control arm. These findings require further investigation.

As further evidence of the marked effect of ulnar nerve block on the paralysis induced by decamethonium a nerve block was carried out immediately after the onset of paralysis. The resulting hyperæmia produced a rapid recovery from the paralysis whereas the control arm remained paralysed (Fig. 9).

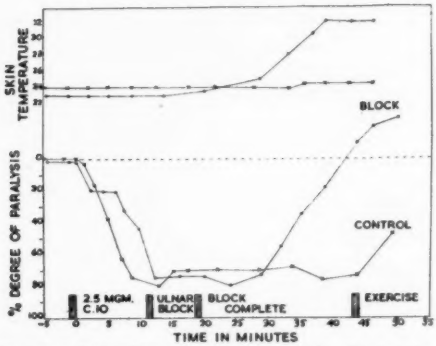

FIG. 9.—The effect of a post-paralysis ulnar nerve block on paralysis following decamethonium.

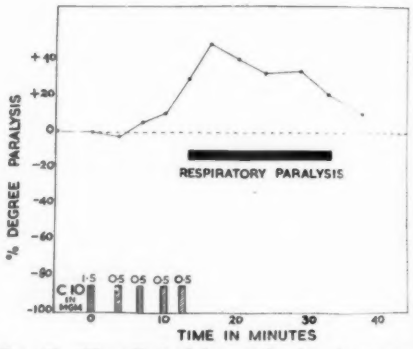

FIG. 10.—The effect of decamethonium in a severe case of myasthenia gravis.

From this evidence it seems clear that the duration of paralysis following decamethonium is largely related to the blood supply of the part being studied. The importance of this will be realized when it is recalled that the blood flow through a muscle during exercise may be over twenty times more than the flow during rest.

Although we have studied only one group of muscles throughout (those of the hypothenar eminence), the relation of the paralysis produced by decamethonium on this group of muscles to its blood supply suggests that the constantly active respiratory muscles should be the last to be affected and the first to recover.

Guild (1950), using an ergometer and cyclometer, states that his subjects recovered more quickly than those quoted by Organe (1949) who used an ergometer alone. It seems possible that Guild's subjects may have undertaken more strenuous exercise, resulting in an increase in muscle blood flow, and consequently a quicker recovery from the effects of C 10.

Again, Gray (1950) states that the use of decamethonium for long operations has been discontinued because of the occasional prolonged paralysis due to delayed detoxication. It has now been shown that the peripheral blood flow is greatly increased at the beginning of anæsthesia (Lynn and Shackman, 1951). However, after the first hour the blood flow has returned to normal and later may be seriously reduced. It is thus possible to imagine that the use of decamethonium towards the end of a long abdominal operation with some degree of peripheral vasoconstriction may be followed by a very prolonged paralysis. In the event of continued respiratory depression it would seem theoretically sound to use the phrenic pulsator, since the resulting exercise should shorten the duration of paralysis.

Paton and Zaimis (1950) have drawn attention to the danger of comparing the effects of muscle relaxants on the hand-grip muscles and the abdominal musculature. They have pointed out that the two different types of muscle (red and white) respond in different ways to this drug in animals. They also stressed the danger of using conscious volunteers, in whom adrenaline may alter the response of a particular muscle to the injection of decamethonium. We do not believe that the liberation of adrenaline significantly altered the response in our series of control subjects. Adrenaline increases the cardiac output and dilates the muscle vessels, thus increasing their blood supply; consequently, if adrenaline liberation affected our results it would have tended to shorten the duration of paralysis.

(4) *The action of decamethonium iodide in myasthenia gravis.*—Paton and Zaimis in their paper (1950) on the clinical assessment of drugs which produce neuromuscular block stated "it would be of great interest to know what the sensitivity of a myasthenic is to decamethonium, since it would not only determine whether idiosyncrasy of this kind occurred to decamethonium but would also throw light on the pathogenesis of myasthenia". In addition the possible use of decamethonium for the operation of thymectomy demands a full knowledge of the reaction of myasthenics to this drug.

In a series of 14 control subjects and 11 myasthenics Churchill-Davidson and Richardson (1952), using the above technique of administration and measurement, showed that none of the control subjects were able to tolerate 2·5 mg. of decamethonium without showing 60% or more paralysis of the hypothenar muscles as measured by the electromyograph, and indeed only one tolerated 2·0 mg. without showing a marked degree of paralysis. In contrast, the 11 cases of myasthenia gravis showed, with only one exception, a marked tolerance to the paralysing action of decamethonium iodide. This tolerance reached its extreme in one patient who after an injection of 10 mg. of decamethonium iodide showed no signs of a response. This case is more remarkable not only for the fact that it suggests a high degree of tolerance to decamethonium but that the depth of that tolerance has not yet been sounded.

If the only evidence of myasthenic weakness is drooping of the eyelids then that patient is more liable to withstand large doses of decamethonium than one with a more generalized weakness. However, when the limit of this tolerance is reached, it seems that the muscles first affected are those which show the greatest degree of myasthenic fatigue. It is in this fact that the danger of the administering of decamethonium to patients with myasthenia gravis lies, because no longer are the respiratory muscles necessarily the last to be paralysed. For example, one patient with severe myasthenia gravis was given 3 mg. of decamethonium, there being at this stage only a slight visual disturbance with hoarseness of the voice. Immediately after giving a further 0·5 mg. complete paralysis of sight, voice, swallowing and respiration ensued. However, the patient was still able to signal with his arms. In fact, electromyographic measurements showed an increase in the response of the hypothenar muscles. Thus, paradoxically, a patient with complete bulbar paralysis was not paralysed in his peripheral muscles (Fig. 10).

The significance of these findings in myasthenia gravis from the anæsthetist's viewpoint is that should a patient with latent or a subclinical degree of myasthenia receive a large dose of decamethonium iodide in error, then the response is unlikely to be as great as that of a normal subject. If the dose was great enough to paralyse the patient's respiratory muscles, however, then the evidence suggests that the duration of the respiratory paralysis would depend chiefly upon the rate of excretion of the decamethonium.

It is a pleasure to acknowledge the help we have received from Dr. P. Bauwens and Dr. M. D. Nosworthy, of St. Thomas's Hospital.

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Dr. W. D. M. Paton: Drs. Churchill-Davidson and Richardson appear to have established decisively three points:

(1) That myasthenics may be resistant to decamethonium.

(2) That the blood flow to a limb alters the intensity of neuromuscular block produced by decamethonium.

(3) That decamethonium excites not only muscle fibre activity but also motor unit activity.

(1) There has been, possibly, some misunderstanding about the relationship between *d*-tubocurarine and decamethonium. The experimental background was as follows: we showed (Paton and Zaimis, 1949) that decamethonium had many radical differences in action from *d*-tubocurarine. Zaimis (1951) demonstrated how closely the stimulant actions of decamethonium were paralleled by those of acetylcholine itself, and concluded from her analysis that decamethonium was acting like acetylcholine, in contrast to the acetylcholine-antagonizing action of *d*-tubocurarine. Burns and I (1951) showed that decamethonium depolarizes the end-plate region just as acetylcholine does, and, further, that this depolarization (which, if transient, simply excites) will, as it persists, cease to excite and produces instead a condition of electrical inexcitability of the end-plate region. *d*-Tubocurarine produces no changes in potential at the end-plate but prevents the action of depolarizing agents.

These fundamental differences result in the general situation that those conditions (summarized by Paton, 1951) which favour the action of *d*-tubocurarine lessen the action of decamethonium, and vice versa.

The possibility was, therefore, that a myasthenic, in whom, as we know, *d*-tubocurarine is peculiarly active, should not only fail to be abnormally sensitive to decamethonium, or even merely exhibit normal sensitivity, but should actually be more resistant to decamethonium than normal individuals. It is this point that Churchill-Davidson and Richardson have appreciated and demonstrated so convincingly. It must be added, of course, that there is likely to be a rather complex relationship between the intensity of the myasthenia and the sensitivity to decamethonium. If one can use the analogy of the partially curarized organism, then, in general, one would expect actual resistance to decamethonium to be most easily demonstrable in the milder cases of myasthenia.

It follows, then, as the authors have pointed out, that the end-plate of the myasthenic is resistant to depolarization. If myasthenia is not due to a circulating curarizing compound (and the curious incidence of its attack in the body is often extremely unlike the uniform picture to be expected with a blood-borne blocking agent), then one must suppose that there is in the muscle membrane at the end-plate some defect of the specific apparatus whereby the impact of minute amounts of acetylcholine arouses a potential change big enough to excite the muscle fibre.

(2) The effects of changes in muscle blood flow on neuromuscular block by decamethonium are quite new and most important. I would like to know what would be the outcome of similar experiments with *d*-tubocurarine, and such experiments might well exclude some of the possible explanations. One suggestion may be ventured, however. As already mentioned, decamethonium causes a persisting depolarization of the end-plate, and with this depolarization (as with that of any other of the excitable membranes in the body) there will be a passage of potassium outwards. Now Hodgkin and Huxley (1947), in early work on ion-movements, were able to measure the amount of potassium released by an action potential in a non-medullated nerve by enclosing the nerve in liquid paraffin, so that the potassium was released into the very thin film of saline left round the nerve and could accumulate in a concentration sufficient to alter the properties of the nerve membrane quite considerably. As soon as the nerve was rinsed in saline, these effects disappeared.

I suggest that perhaps there is an analogous situation here. In the relatively avascular muscle, potassium accumulation in the environs of the depolarized end-plate must certainly be occurring, and might well accentuate the inexcitability of the membrane; whereas such accumulation would be much slighter in well-vascularized muscle. One can then explain one curious feature of their results, that procaine nerve block was a more effective antagonist than exercise. For muscular exercise, while increasing blood flow, will also itself cause the release of potassium from the muscle fibre, but the release of sympathetic constrictor tone by procaine block will not do this.

The other aspects of these findings should make us look at many of the experimental results in a new light.

(3) The excitation of motor-unit activity may, I think, be attributed to an action described by Masland and Wigton in 1940. They observed that the fasciculations seen in cats after the injection of Prostigmine were associated with impulses travelling antidromically up the motor nerve towards the ventral roots, and that these impulses were abolished by curare, but could also be obtained with acetylcholine. They excluded the possibilities that the effect was due to stimulation of the motor nerve endings by movements of the muscle, or to stimulation of the nerve trunk directly by these drugs, and verified that the impulses were running centripetally. Their tentative conclusion was that acetylcholine can stimulate nerve terminals as well as end-plates, but this is somewhat uncertain.

Since acetylcholine, prostigmine and decamethonium are all so closely related in their actions at the end-plate, one may accept very readily Churchill-Davidson and Richardson's conclusion that they have been observing synchronous discharges by motor units, and suggest that these discharges correspond to the Masland-Wigton phenomenon, in which excitation of some of the nerve terminations of the motor unit causes a centripetal antidromic impulse in the motor nerve axon and (by a sort of "axon reflex") a more or less synchronous discharge of the whole motor unit.

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Dr. A. R. Hunter (Manchester): Drs. Richardson and Churchill-Davidson have found that the mildly myasthenic patient is extremely resistant to decamethonium while the patient severely affected by the disease is only slightly more resistant than normal. There is an analogous state of affairs in mice curarized with gallamine triethiodide (Flaxedil): those which have nearly completely recovered from the effects of this agent have an appreciably increased resistance to lethal doses of decamethonium whilst animals still profoundly paralysed by the gallamine triethiodide gain no protection from this fact.

Is it possible that penta- and hexamethonium owe their somewhat unsatisfactory antagonism to decamethonium simply to the fact that they are vasodilators, and that they have no real power of directly reversing the paralysis produced by decamethonium?

We have been told that contracting muscle requires a relatively large amount of decamethonium before it becomes paralysed. Is this the cause of the divergence of opinion concerning the value of this drug? Where a relaxant of this kind is used with anæsthesia so deep that spontaneous respiratory contractions of the flat muscles of the abdomen do not occur, then decamethonium will produce a very satisfactory degree of flaccidity of the abdominal wall: if, however, the covering anæsthesia is light then satisfactory relaxation is not so likely to be obtained.

Section of Surgery

President—DAVID H. PATEY, M.S., F.R.C.S.

[*December* 5, 1951]

DISCUSSION ON THE TREATMENT OF LARGE HERNIÆ

Mr. Geoffrey Keynes: By the term "large herniæ" I mean really large ones, and it is of these only that I shall speak. (Examples of very large herniæ—inguinal, sliding inguinal, femoral, ventral and umbilical—were illustrated by lantern slides.)

There are, practically speaking, no herniæ too large for cure by surgery—with very occasional exceptions. (One of these was illustrated.)

A dangerous type of patient is the extremely obese individual with no space to spare in the abdomen. I have operated on one such in whom the reduction of an incisional hernia consisted only in the replacement of omentum. He died very soon from intestinal obstruction. The omentum should have been removed.

Another principle is that there is no patient nowadays who is too old to be treated by surgery. Most of us are accustomed to facing the ordinary problems of geriatrics. More than thirty years ago I became attached to the City of London Truss Society and during eleven years saw between ten and twelve thousand patients with hernia. Many had been filtered through hospital clinics and were regarded as being unsuitable for surgery. Often they were old, and very unhappy with uncontrollable herniæ. I took pride in dealing at St. Bartholomew's with many patients whom at that time no one else would touch. One of our earliest problems was a man with a very large deficiency in the posterior rectus sheath. This we successfully closed by inlaying a sheet of fascia lata 15 × 10 cm. Large "sliding herniæ" were frequent, but the problem of the sliding hernia is not really particularly difficult if the method of repair is sound. The large femoral herniæ were always recurrent herniæ following relief of strangulation by destroying the lacunar ligament, a quite unnecessary procedure. The largest ventral herniæ were almost always following gynæcological operations.

In 1925 Professor W. E. Gallie introduced new details in the technique of fascia-lata grafts, particularly the bootlace technique for ventral herniæ, using a double strip united at one end. This method draws the whole length of the deficiency together in a single line without great tension. After many years' follow-up we were satisfied that there were very few failures except among the large umbilical herniæ in obese women. In these every technique was tried, but none was entirely satisfactory.

Later on I used the McArthur technique in the inguinal region; this is really a Gallie technique on a small scale.

I have believed firmly in the principle of using the patient's own tissues whenever possible, and have avoided the use of any foreign bodies whether floss silk, silver filigree, steel wire, vanadium gauze, or any other. These depend partly on the creation of scar tissue for the cure of the hernia, and this I believe to be surgically unsound, apart from the danger of immediate or late infection. The real principle to be observed is the meticulous removal of all scar tissue, and the anatomical re-apposition of healthy tissues, with the least tension, using natural materials. Some of the supposed advances have really been retrograde, and many patients have suffered in consequence.

Mr. Ivor Lewis: A large hernia may be defined as being the size of a man's fist, whereas a hernia as large as the human head may be described as a huge hernia.

I shall confine myself to inguinal, femoral, umbilical and ventral, omitting the rare herniæ, and also the diaphragmatic.

These four varieties of hernia may be either primary or recurrent. Other things being equal, the recurrent cases always carry a poorer prospect than the primary, and strangulated ones the worst of all. Of these, incisional ventral herniæ are of peculiar importance to the surgeon as their very occurrence is a reproach to his craft.

For some years now, I have tried not to reject anyone seeking relief from a hernia, merely because it is large, or because it is recurrent, or because the patient is fat and flabby.

The treatment of large herniæ differs from that of small herniæ in four ways.

(1) *The skin.*—Most patients with large herniæ have intertrigo. Some of the bad cases take a few weeks for this to be cleared with twice daily baths, and careful drying and powdering.

At the operation the under surface is not touched, swabbing with skin lotion being confined to the exposed aspect. The incision is made on this surface and skin towels immediately sutured to the edges. At the end of the operation I make no attempt to excise redundant skin—purposely leaving this to a later date. Actually by then it is hardly ever necessary.

(2) *The dissection and reduction of the contents.*—This is sometimes surprisingly easy; the greater part of the gut may be present in the sac without a single adhesion. Usually, however, one must be prepared for perhaps an hour's work in the liberation alone.

If there is voluminous and inspissated omentum adherent in the sac, it is as well to resect it. I have never resorted to resection of any other content, and I have not yet met a hernia which had "lost its domicile". If I ever do, my plan will be to repair the hernia in 2 stages; this is sometimes possible. If not, it is to make a counter-incision in the anterior abdominal wall, mobilize the transverse colon and splenic flexure, and bring the colon out through the wound, to be resected in a few days' time in the manner of Mikulicz, after the hernia wound has healed.

Perfect relaxation is a paramount necessity. At one time this luxury was limited to the best anæsthetists but in these days of curare, it is surely within the reach of even the poorest.

(3) *The closure of the abdominal wall.*—The first thing that surprised me about the *huge* herniæ was the comparative smallness of the actual gap in the abdominal wall. Except for ventral herniæ, it seldom admits more than the four fingers. The difficulty about closing a wound of such a size is, therefore, very little, provided again that we have perfect relaxation, that we suture carefully and refuse to be intimidated by the spermatic cord.

Repair should be based on clean dissection of the edges of the gap, followed by straightforward and painstaking suture. In other words we must not become slaves to some fashion in place of simple craftsmanship. Filigrees, fascial sutures, fascial flaps, cutis grafts, floss silk and nylon darns are only very occasionally necessary. Fortunately when it comes to the cure of *large* herniæ we are spared the polemics which have raged against the Bassini operation, as there is no question of "preserving the delicate mechanism of the inguinal canal".

Normally the surgeon relies on clean definition of muscle edges, thorough removal of loose fat and areolar tissue, suture of the apposed or overlapped edges with interrupted and non-absorbable sutures. In other words the cure of the hernia depends, more than anything else, on good honest cobbling.

(4) *Having reduced and repaired the hernia, will the sudden rise of abdominal pressure affect the patient*?—The only caveat here is that huge hernia cases with a low vital capacity from bronchitis or cardiovascular disorder should not be operated on unless the hernia is strangulated.

In the healthy subject I have not yet come across a case in which it was impossible to reduce the contents within the abdomen, or in which the patient was unable to adapt himself to the change. In other words I am not sure there is such a thing in practice as a hernia which has "lost its domicile".

The recent common use of *pneumoperitoneum* for the treatment of pulmonary tubercle has given us some useful information on intolerance to sudden increases in intraperitoneal pressure.

In the adult 1,200 c.c. are barely noticed, whereas 2,000 c.c. cause some discomfort.

There are very few herniæ of more than 2 litres in volume. In doubtful cases I recommend estimating the volume of the hernia, and then carrying out a trial pneumoperitoneum of the same volume.

Some Special Points

(*a*) In *large inguinal herniæ*, both direct and oblique, I have come to do one operation only—the strict Bassini, occasionally supplemented by a Tanner release, and frequently finished by transposing the cord to the subcutaneous plane.

I like fine interrupted sutures, usually nylon or indeed any other material provided it is not catgut.

(*b*) In *large femoral herniæ* I like the high operation, reinforcing the gap if possible by suture of conjoined tendon to Cooper's ligament, preferably by McEvedy's method.

(*c*) *Umbilical herniæ.*—The Mayo operation: combined with panniculectomy.

(*d*) *Ventral herniæ.*—Though dissected anatomical layers are admirable in some cases, e.g. gridiron scar hernias, for mid-abdominal ones, I am coming to favour more and more the single solid edge overlap method. This is the application of the Mayo operation to ventral hernias.

Its advantages are (1) economy of tissue and avoidance of too tight an abdominal wall; (2) ample strength, especially if overlapped.

I like the closed or invagination method in certain cases. In this the peritoneal cavity is not opened—the stretched piece of hernial wall being merely invaginated and the strong rectus edges sutured carefully with a row of interrupted silk or nylon sutures (Fig. 1).

In some cases of ventral hernia or divarication I have employed what may be styled the fascial interdigitation method (Fig. 2). It is very strong and uses fascia which remains living and fully nourished.

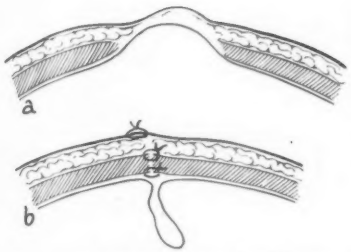

FIG. 1.—Showing inversion operation of ventral hernia.

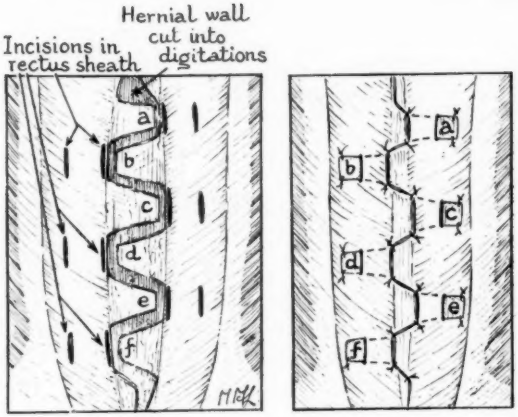

FIG. 2.—The interdigitation method of bracing.

(*e*) *Orchidectomy*.—Old men with large inguinal herniæ, especially if strangulated, should always be told that an orchidectomy may be necessary. We may then be practically certain of a sound repair. Only in the worst cases is orchidectomy actually done, and in the others I thin the cord, removing all its coverings including cremaster, all the fat, and most of the spermatic venous plexus. This leaves a cord the thickness of a pencil. To complete the security measures, the cord is transposed subcutaneously, so that the external oblique can be sutured down into one solid sheet with the rest of the inguinal muscles.

(*f*) *Sliding herniæ*.—The treatment here is to *slide* them back. It is not necessary or desirable to open the irrelevant little sac which lies in front. The abdominal wall is then reinforced in the usual way.

Occasionally it is a help to make an incision into the peritoneal cavity higher up and pull the colon up, as recommended by Roscoe Graham.

(*g*) *Strangulation* is the only imperative indication to operate on large or huge herniæ.

One special point is worth making here: that if the patient is very ill and the hernia very large, it may be worth while to relieve the strangulation and do nothing else at the time. The cure of the hernia can then be undertaken later, with safety and much greater prospect of success.

CONCLUSION

Over the past few years I have been operating on some 25 large herniæ a year, with three or four huge ones. There have been two post-operative deaths, one from ileus, in an obstructed hernia, and one from a stroke eight hours after the operation. The other cases have been well worth doing. From being seriously disabled, they have been made into comfortable, useful, and even productive members of society. Owing to their age it has not been possible to follow up all of them but certainly 4 out of 5 are known to have been free of recurrence during the first two years—admittedly a short time, but most of the *bad* recurrences will appear during this period.

In the subsequent discussion **Mr. G. E. Moloney** said that para-umbilical hernia frequently results from stretching of tissues due to high intra-abdominal pressure from accumulating fat, and that incisional hernia is frequently aggravated also by increasing adiposity. In such patients, if the hernia is very large, the first line of attack should be to encourage reduction in weight; if such is not possible they should be treated by a corset with a bucket appliance. In any operation he (Mr. Moloney) freshened the edges of the aperture and approximated them with layers of continuous nylon. In inguinal hernia he used a nylon darn. He preferred to use a darn in the repair of herniæ of any size. The darn should be tailored for the individual, of small mesh, well anchored to sound surrounding tissues, of good pliant material (nylon does not kink in the darning nor does it fracture at a later date), which produces minimal tissue reaction, is technically simple to introduce, and tends not to be disturbed by the misfortune of sepsis. He preferred monofilamentous nylon to braided nylon. **Professor P. B. Ascroft** confined his remarks to the use of tantalum gauze in inguinal hernia and spoke not as an advocate of tantalum but merely as an observer of results. These results were good. A few of the inlays fractured. About six months was the time after which one might expect a fracture to take place. **Mr. Henry Thompson,** in speaking of the effects of foreign bodies in the tissues, said that the suture materials which were now manufactured did not contribute to sepsis *per se*. If sepsis occurred with their use, it was introduced by the faulty technique of the surgeon and to attribute it to any particular material was quite illogical.

Mr. Norman Tanner thought that there was overmuch talk of the necessity to have some foreign body obturator to close the opening left by a large hernia. He thought there was practically no inguinal hernia which could not be closed by using adjacent tissues, for example the "slide" operation. **Mr. M. R. Ewing** suggested that there were some large incisional herniæ where the defect in the abdominal wall was so large as to make them incurable by any method of repair. **Mr. E. T. C. Milligan** referred to the big herniæ sometimes seen in a colostomy wound. These could be dealt with easily by dissecting out the colostomy stump, closing the wound, and bringing the colostomy through a stab wound above the original colostomy opening. **Mr. G. Qvist** referred to the use of floss silk which in his hands and those of his senior colleague, Mr. Rodney Maingot, was very rarely associated with sepsis, which had been the main criticism of the method. **Mr. Maurice Lee** thought it wise, in operating on large herniæ, particularly in fat people, to have the patients admitted at least a week beforehand for prophylactic treatment with penicillin and streptomycin. He thought there was nothing better than the Mayo operation in umbilical hernia and deprecated Nuttall's operation for large ventral hernia. **Mr. A. K. Monro** advocated the lattice type of repair, the chief feature of which was not the material that was used but the type of repair itself.

The President, at this point, summed up the discussion so far as it had proceeded: What had emerged from the discussion was that the surgeon must not be put off by the size of a hernia, by its complicated nature or by the age of the patient. There was also agreement that with these large herniæ the problem of the breakdown of the functional mechanism in the first instance was academic, and the strongest emphasis seemed to have been laid on the fact that large herniæ could be reduced to clefts and so be repaired. Although the hernia might be very large, the cleft through which it came might be very small. Something had been said about tantalum, and from Professor Ascroft's and Mr. Ewing's contributions the disadvantage of tantalum because of its tendency to break down had been evident. This had not solved the problem of filling a gap, if there was really a gap the edges of which could not be approximated. About materials, the patient's own tissues and other tissues had been mentioned and a strong case had been made out by Mr. Qvist for silk and by Mr. Moloney for nylon. Particularly in the case of nylon—and the point had been brought out again with tantalum by Professor Ascroft—the advantage had been mentioned that the material might be used in spite of a mild degree of sepsis.

Mr. Harold Dodd advised operation for hernia without exception for all people over the age of 50. He made a plea for local anæsthesia combined with a general anæsthetic. **Mr. Alan Hunt** thought that stainless steel was the safest material wherever sepsis was likely but this did not necessarily mean that this was the best material in all cases. The important thing was that healthy tissues should be approximated without tension.

Mr. Geoffrey Keynes, replying to the discussion, said that a good many of the speakers had not really been talking about large herniæ but about herniæ in general. That subject admitted of an enormous number of variations in technique, but he found himself in substantial agreement with Mr. Ivor Lewis, whose guiding principles accorded very much with his own. On the question whether the Gallie graft lived or not, he believed animal experiment had shown that it did live. Integrity of repair did not depend so much on the strength of the graft but on its remaining alive long enough to enable the tissues to approximate and to remain approximated. The graft itself was not the essential thing, the question was whether, without tension, the modern form of graft remained alive long enough. Many points had been raised in the discussion. Mr. N. Tanner had mentioned that he had used his (Mr. Keynes's) modification of the Hoguet operation. What he had done for many years was to use the slide rather than the turn-over of the flap. It was difficult to answer criticism such as had been put on the screen based on the figures of an individual operator; one did not know what technique had been used. To make an incision in the rectus sheath and achieve approximation without any tension at all was a very important part of the procedure, and a modification of the original McArthur operation had that in view.

Reference had been made to the use of local analgesia. He himself had carried out operations on many of the largest herniæ with local analgesia, which was of great value, especially in the days when ether was still being used. Now that they had curarè as the alternative, probably local analgesia could be used rather less; it was time-consuming and perhaps did not give as good relaxation as curare. Obviously the reduction of these enormous herniæ depended very much on relaxation. Mr. Moloney's remarks on nylon were open to the criticism that any technique adopted should not involve the subsequent necessity of taking anything out. The same criticism applied to floss silk; this material in expert hands would produce excellent results, but unless it was used by masters of technique it might lead to terrible disasters; therefore it was not a suitable method for general use. He could not, however, criticize it on a personal basis because he had never used it; he had heard so much about it that he felt he need not himself make the experiment. Lastly, he took up the remark of the President about filling the gap. He thought the answer was that it was very seldom that a gap had to be filled, because, if the principles which he had already expounded were carried out, in almost every case edges of healthy tissue could be approximated. In the rare case of a large gap which had to be filled in, possibly some form of lattice darning would be necessary.

JOINT MEETING No. 2

Section of Surgery with Section of Urology

Chairman—DAVID H. PATEY, M.S., F.R.C.S.
(President of the Section of Surgery)

[*January* 8, 1952]

DISCUSSION ON THE TREATMENT OF CARCINOMA OF THE BLADDER

Mr. E. W. **Riches** (Middlesex Hospital):

INTRODUCTION

I shall base this general survey of the treatment of malignant disease of the bladder on a series of 302 personal cases treated over the past twenty-one years. I have excluded patients treated by X-rays alone, and a few who for various reasons were not treated at all. I have not included any cases of benign papilloma (although it is generally recognized as the first stage of carcinoma).

GENERAL CONSIDERATIONS AFFECTING THE CHOICE OF TREATMENT

The choice of treatment depends on many factors. In a condition occurring most often in the seventh decade of life and at ages varying from 23 to 90 years (in this series) the general condition of the patient may determine the choice to some extent. If he is considered medically suitable for any chosen method the size, situation, multiplicity, gross characters, and histological type and extent of spread of the tumour as well as the degree of renal damage will all have a bearing on the final selection. It will not necessarily be final but must be changed or combined with other methods according to progress; surgery and irradiation must work in collaboration not competition.

INVESTIGATION

Complete diagnosis demands certain special methods of investigation in addition to a routine clinical examination. They include cystoscopy, biopsy of the tumour, bimanual pelvic examination under full anæsthesia, and intravenous pyelography.

Cystoscopic biopsy.—Pathology forms the basis of treatment, and so biopsy will be considered first. Pieces of the growth are removed by Lowsley's forceps, or by a McCarthy loop. There are some fallacies, and some possible dangers.

To compare the results of treatment there must be a system of pathological classification. I have adopted the classification described by Dukes and Masina (1949). It recognizes three grades of malignancy based on cell differentiation and designated grade I or low, grade II or average, grade III or high. Broders (1922) described four grades, and Franksson (1950) of Stockholm recognizes seven grades. Figures of survival by grades suggest that a low grade (I) and a high grade (II and III) might be sufficient for our purpose. Providing the grading is done by an experienced pathologist the system is of considerable value in deciding treatment, and assessing prognosis; for example my three-year survival rate after partial cystectomy was 69% in grade I cases and 30% in grades II and III.

In addition to grades this classification includes stages based on an estimate of the extent of spread of the tumour. In stage 1 it is confined to the bladder; 1A indicates limitation to the mucosa or submucosa, 1B spread into the bladder muscle. In stage 2 there is extension into the perivesical fat and in stage 3 paravesical lymphatic glands are invaded. Stage 4 describes those tumours, mostly inoperable, in which there are remote metastases which cannot be removed in continuity with the main growth.

Cystoscopy.—Fortunately for the clinician the cystoscopic appearance usually gives a good idea of the degree of malignancy of the growth, but after the preliminary out-patient diagnostic cystoscopy the examination should be repeated under anæsthesia if an accurate assessment is to be made. Biopsy and bimanual examination can be done at the same session. In general it will be found that the fronded papillary tumours, although often of large size, are of low malignancy; the solid nodular tumours are more invasive, whilst the ulcerative tumours are of the highest degree of malignancy. A tumour may change its type in the course of time and one which is first seen as a papillary growth of low grade may reappear as a solid carcinoma of grade II or III. Moreover tumours of different types

are sometimes found together in the same bladder, and there is ample evidence of this tendency to greater malignancy after inadequate treatment.

The cystoscopic appearances of the various types can best be illustrated by some photographs of total cystectomy specimens, which will also show the indications for performing that operation. They are shown in progressively increasing degrees of malignancy.

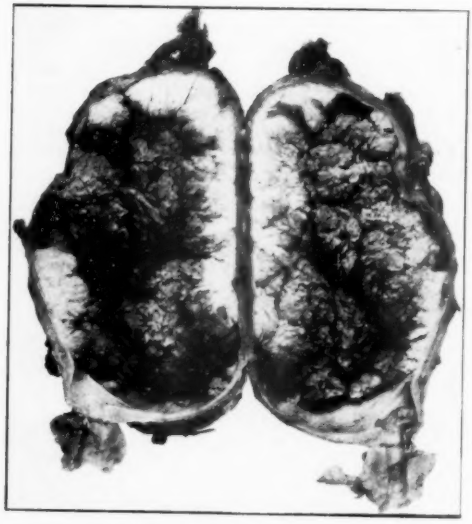

FIG. 1.—Diffuse papillary carcinoma, grade I, stage 1A.

FIG. 2.—Solid nodular tumour with mucosal changes beyond it, grade III, stage 1B.

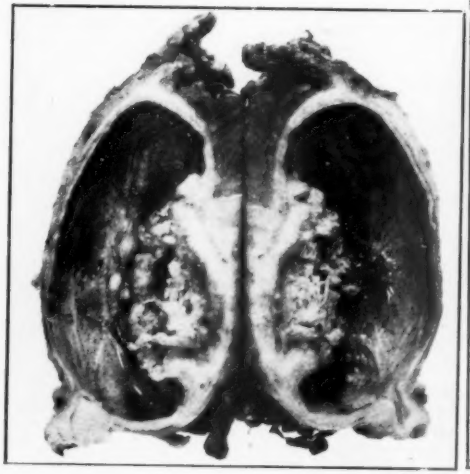

FIG. 3.—Nodular tumour with deep surface ulceration, grade III, stage 4.

FIG. 4.—Ulcerative carcinoma, grade III, stage 4. The lesion is purely destructive and shows no intravesical projection.

Fig. 1: Diffuse papillary carcinoma, grade I, stage 1A, in a woman of 42, treated elsewhere by cystodiathermy and twice by open diathermy over a period of four years. (Alive and well two years after cystectomy.)

These are often low-grade tumours of long standing in which there has been failure to control the growth by cystodiathermy.

Fig. 2: Solid nodular tumour with surface ulceration and mucosal changes beyond the tumour, grade III, stage 1B. Palpable bimanually and producing dilatation of the right ureter. (From a man of 56 who is alive and well nearly two years later.)

Fig. 3: Diffuse large nodular tumour with deep surface ulceration, invasion of paravesical fat, and deposits in the external iliac glands which were removed at operation. Grade III, stage 4. From a young man, aged 40, treated by cystodiathermy for a year. Although the prognosis appeared hopeless, cystectomy was carried out to relieve pain, hæmaturia and incontinence. (Death from pelvic recurrence five months after cystectomy.)

Fig. 4: Ulcerative carcinoma, grade III, stage 4. From a young woman of 36. The right kidney had been removed for pyelonephritis twelve years before and the present pain and hæmaturia were thought to be due to tuberculosis. The correct diagnosis was made by cystoscopic biopsy. The two right ureters, bladder and uterus were removed together with a mass of invaded glands in the right side of the pelvis. A full course of X-ray treatment was then given. She is alive six months later and the palliation has been worth while, but she has a large pelvic recurrence and glands invaded in both axillæ.

This is the most lethal form of bladder cancer, which starts as a malignant ulcer with no papillary stage.

Bimanual pelvic examination with complete relaxation under anæsthesia is an essential investigation. A tumour which is palpable has usually, but not always, spread into the muscle; a tumour which is fixed is inoperable.

Radiology.—Intravenous pyelography should be included in the investigation of every case of bladder cancer. It may reveal an unsuspected primary growth in the renal pelvis, and it will show dilatation or poor renal function better than other tests. A cystogram will sometimes give a good idea of the extent and nature of a growth. An X-ray of the chest should not be omitted.

Methods of Treatment Used

There are many ways of treating carcinoma of the bladder; Table I shows the methods employed in this series. Many patients were treated in more than one way and so some are included under more than one heading. The methods are divided into (1) purely surgical, (2) combined surgical and irradiation, and (3) irradiation alone; I am leaving methods of pure irradiation to later speakers but would point out that deep X-ray treatment was added to surgical treatment in 38 or 13% of the patients. Whatever method is chosen it is important to explain to the patient at the outset that he must be prepared to come for regular follow-up examination for many years; I would like to make this a condition before treating him at all.

Table I.—Treatment Used in 302 Cases

	Cases	Percentage of whole
Surgical:		
Cystectomy Total	69	23
Partial	61	20
Cystodiathermy..As main method	40	13
..Combined with other methods	123	41
Open diathermy excision	21	7
Palliative ureteric transplantation	36	12
Irradiation:		
Radon	63	21
Radium	15	5
Open X-ray	12	4
Deep X-ray added to other treatment	38	13

Table II.—Survival Rate of 302 Cases from the Time of Seeking Treatment

Years	Survivors	Percentage
1	128/270	47
3	72/200	36
5	53/147	36
10	16/56	29
15	6/31	19

32 patients treated less than one year. The figures in this and the other tables indicate the actual survivors and the possible survivors for the period concerned.

Survival

Table II shows the average survival of all cases irrespective of type or method of treatment from the time of their first attendance. Of every 100 cases only 47 are alive at the end of a year, but 36 are still alive at five years, at ten years the percentage alive is 29, and at fifteen years 19. The more malignant cases die early, the less malignant live long. It is the interval between the onset of hæmaturia, the presenting symptom in 95% of cases, and the starting of treatment which has the greatest bearing on the expectation of life.

Individual Methods of Treatment

A. Surgical

(1) *Total cystectomy* offers the most radical means of extirpating the growth and its immediate extension, but it carries with it the need for deviation of the urine either into the large intestine or on to the skin; the former is preferable. The operation can be carried out in one, two, or three stages and in the last three years I have done it in a single stage in 75% of cases and in two stages in the remaining 25%. It is most likely to succeed in the papillary tumours of low-grade which are too extensive to be cured by other methods.

The main indications for the operation may be summarized:

(*a*) Multiple, extensive, or widely separated tumours of low malignancy, too large to be successfully treated by other means.

(*b*) Tumours situated on the base of the bladder.

(*c*) Single tumours of higher malignancy showing evidence of mucosal change beyond the apparent margin of the growth.

(*d*) Cases where the bladder capacity is already very small.

(*e*) As a palliative procedure where other methods have failed or appear unlikely to succeed.

As long as the last group forms the main bulk of cases submitted to total cystectomy the figures of long-term survival are not likely to be impressive; this was so in most of my earlier cases, and my figures of only 9% five-year survivals from the date of operation in 69 patients (Table III) are an index of this fact, for the subsequent deaths were due to recurrence or metastasis in 44% of cases. The table also includes, without distinction, 5 cases where the bladder cancer was secondary to a growth in the uterus, large intestine, kidney and ureter or urethra. Of the 25 (40%) one-year survivors 9 have already passed the two-year mark. The five-year survival for grade I cases was 18%, and for grades II and III nil.

Uræmia accounted for 25% of the late deaths, and obstruction of the ureter whether before or after the transplantation is serious. The power of recovery of an obstructed kidney depends on the length of time the obstruction has existed. If the ureter is not grossly thickened and there is some kidney function transplantation is well worth while and some recovery may be anticipated. If one kidney is infected and functionless it is better removed, but occasionally a temporary nephrostomy will produce sufficient improvement to make transplantation possible.

The operative mortality was 11·6%, being 16% for single-stage operations, 11% for two-stage and 7% for three-stage. This should not deter a one-stage operation in a suitable case; it has many advantages. If total cystectomy appears to be the method of choice it must be done early before renal damage or extension of the growth spoils its chances of success. It should not be reserved for the hopeless cases.

Table III.—Total Cystectomy

Survival in 69 Cases

Years	Survivors	Percentage
1	25/62	40
3	4/37	11
5	2/23	9

Operative mortality 8/69 = 11·6%.
7 patients operated on less than one year ago.

Table IV.—Partial Cystectomy

Survival in 61 Cases

Years	Survivors	Percentage
1	38/55	69
3	26/52	50
5	17/45	38
10	5/24	21
15	1/11	9

Operative mortality 6/61 = 9·8%.
6 patients treated less than one year.

(2) *Partial cystectomy* or segmental resection was done in 61 cases with 6 deaths, an operative mortality of 9·8%. It is reserved for single localized tumours with no evidence of mucosal change beyond them. Tumours of the vault are most accessible and I have not found that they are more prone to metastasize than those of the base. The whole thickness of the bladder wall must be removed with a margin of at least an inch (2·5 cm.) of healthy bladder around the tumour. If the ureteric orifice comes within the area to be removed there should be no hesitation in excising it and re-implanting the ureter into the bladder. This was done in 12 cases (nearly 20%), and the results have been generally good, 6 of these patients living more than three years and one being alive and well more than fifteen years later. The survival figures are given in Table IV and show 38% of five-year survivors. Of the 5 ten-year survivors all are still alive and well at periods of ten to fifteen years; 4 had grade III tumours and one a grade II, and none had any other treatment; an early adequate partial cystectomy is still the best treatment for an accessible single growth of whatever degree of malignancy.

Growth in a diverticulum.—There are two special varieties of growth treated by partial cystectomy. I refer first to those arising in a diverticulum. There were 5 such cases of which 4 were of high-grade malignancy and 2 were fixed to the pelvic wall. Fig. 5 shows one of the more favourable specimens from a man of 71 who is alive and well nearly two years after diverticulectomy and prostatectomy.

Urachal growths.—The other special group is the urachal adenocarcinoma seen high up in the dome of the bladder and easily missed on cystoscopy. Its histology should be found by biopsy, and it should

be treated by excision of the umbilicus, urachus and dome of the bladder. I have had 5 such cases and 3 are living over four years so it would not appear to be of extreme malignancy.

(3) *Cystodiathermy* was the main method of treatment in 40 cases or 13% of the whole, but was used in conjunction with or preceding other methods in a further 41%. It has its greatest value in the papillary tumours of low-grade malignancy in elderly patients and it must be thorough. It is a tedious process but it is generally better to destroy a tumour completely in one sitting if possible, and to desiccate its base than to employ multiple short sessions. Follow-up cystoscopy should be done in two or three months; at an earlier stage reactionary œdema obscures the picture. The survival figures

TABLE V.—CYSTODIATHERMY

Survival in 40 Cases

Years	Survivors	Percentage
1	27/30	90
3	16/21	76
5	7/12	58
10	2/4	50

Operative mortality 1/40 = 2·5%.
10 patients treated less than one year.

for cystodiathermy when used as the main method are shown in Table V and the apparent improvement on those of other groups is an index of the type of case selected, the papillary tumour of low or average malignancy. In these the recurrence rate was about 50%, whilst in grade III cases it was 100%. If the tumour is found to be of high malignancy on biopsy radon or some other method should be used instead; in lower grades it is often worth while persisting with diathermy provided always that the patient will continue to attend regularly for cystoscopy so that recurrences may be kept in check. They may appear even after the bladder has been clear for ten years. The operative mortality was only 2·5%.

FIG. 5.—Carcinoma arising in a diverticulum, grade III, stage 1B.

FIG. 6.—Carcinoma of the cervix invading the bladder and rectum with vesico-vaginal fistula. Pelvic clearance.

(4) *Open diathermy* with excision or coagulation after cystostomy is distinct from partial cystectomy. It was used in 21 patients (7%) and the group includes cases at each extreme of malignancy. The best are the multiple or large papillary tumours too extensive for cystodiathermy in patients considered unfit for total cystectomy. The survival of low-grade cases is remarkably good (66%—four cases out of six—at four years in grade I), but regular cystoscopic follow-up is essential as late recurrences are not infrequent; they may sometimes be prevented by adjuvant X-ray treatment.

The worst are the neglected cases of high-grade malignancy and in them the palliation afforded by the open operation is poor, and some of them are made worse. Any open operation on a papillary tumour also carries the risk of dissemination of the growth into the wound.

(5) *Palliative ureteric transplantation* was carried out in 36 cases or 12% of the whole. It affords the best means of saving the patient from a painful bladder death, or a wet death from a fistula, and is worth while when the kidneys are not already too badly damaged. The operative mortality was 23% and the series included 7 cases of secondary uterine cancer invading the bladder, whose end was made more comfortable. The average length of survival after operation was six months. Suprapubic cystostomy is usually the worst form of palliative treatment for bladder cancer. Cordotomy has a place in the relief of severe pain from pelvic metastases, but is apt to be followed by sphincter disturbances. The terminal stages of the uncontrolled disease may be painful and distressing.

Secondary growths in the bladder occurred in 25 cases, forming 8% of the whole. In 9 the primary growth was uterine, in 8 renal (pelvic), in 3 ureteric, in 3 urethral and in 2 intestinal. Some of the uterine cases can be helped by pelvic clearance (Fig. 6) although removal of the rectum with its consequent wet colostomy is not always necessary.

The degree of renal damage is as important in prognosis as the extent of the growth.

Growths arising in the renal pelvis are of diagnostic interest; failure to recognize that the primary growth is renal vitiates treatment of the bladder.

B. Combined Surgical and Irradiation Methods

(6) *Radon.*—I shall say little about irradiation methods but as 63 (21%) of my patients have been treated by radon seeds I will give their survival tables (Table VI). The recurrence rate for low-grade

TABLE VI.—RADON

Survival in 63 Cases

Years	Survivors	Percentage
1	34/48	71
3	14/27	52
5	4/6	66

Operative mortality 4/63 = 6·3%.
15 patients treated less than one year.

tumours was greater than for the higher grades which supports the view that growths of high malignancy are often more sensitive to irradiation than the lower grades.

(7) *Radium* when used inside the bladder is sometimes followed by prolonged cystitis. If it can be placed in the growth from outside this is less likely to happen, and I have used extravesical radium in 8 cases, the first as long ago as 1930; she survived for over three years. It is a useful form of palliation for the solid infiltrating growth which is too advanced for removal.

(8) *Direct X-ray* application after cystotomy was used in 12 cases in the years 1946 and 1947. In two the bladder was rendered tumour free. In any method of irradiation therapy it is an obvious advantage if the surgeon can remove the intravesical bulk of the tumour first unless rays of high penetration can be used.

CONCLUSIONS

In trying to draw conclusions from these cases one problem is at once apparent. Is carcinoma to be regarded as a localized or a generalized disease of the bladder even in its early stages? If the former, then local excision or irradiation should suffice to cure it; if the latter, then the surgical treatment should be total cystectomy, and any form of irradiation should be directed to the whole bladder. There is evidence in favour of localization in the apparent cures effected in some cases by partial cystectomy, but we have all seen cases too in which the whole bladder was studded with tumours at the first examination, and occasional cases where the growth was interstitial, widely infiltrating the whole bladder wall. It seems likely that both conditions can occur, some early growths tending to remain localized at their site of origin in the bladder although extending deeply into and through its muscle wall, whilst others appear to arise spontaneously from multicentric foci in more than one part of the viscus, or at least to spread laterally by lymphatics or blood vessels so rapidly as to make it seem that the tumours have arisen spontaneously. The localised tumours are frequently of the nodular or ulcerative variety and are histologically poorly differentiated, whilst the generalized often appear in papillary form and are well differentiated and of a low histological grade of malignancy. The recognition of such a fundamental difference before operation depends on a careful cystoscopic examination with a search for mucosal changes in the bladder remote from the tumour. Patches of hyperæmia or cystitis, areas of trabeculation, or small nodular elevations should always be regarded with suspicion; one should bear in mind the rapid appearance of skin nodules in carcinoma of the breast when once the growth reaches the lymphatics of the deep fascia and compare it with the submucous spread of papillary tumours of the bladder. Implantation of malignant cells by direct contact of the opposing walls of the empty bladder is another possible mode of dissemination but probably of less frequent occurrence.

It is in the widespread type of growth of low malignancy that methods of general irradiation by isotopes are most likely to supplant surgery; we must also recognize that we cannot yet cure the deeply infiltrating tumour either by surgery or irradiation if it has passed beyond a certain stage, but that we

can often cure it by *early* operation. We must therefore see our cases earlier, which means that we must continue to educate both patients and doctors on the need for cystoscopy in every case of hæmaturia. We must be so equipped that cystoscopy can be carried out expeditiously in properly organized out-patient clinics and we must make the examination in such a way that the patient does not fear to have it done again. Finally every case must be carefully followed up.

I should like to thank Dr. A. C. Thackray and Mr. Masina for the hours they have spent on grading, and all my colleagues for their generous help.

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Mr. Arthur Jacobs (Royal Infirmary, Glasgow): I would emphasise at the outset that although I have been using radium for the malignant bladder over a period of eighteen years, I regard this form of therapy as but one of the methods to be utilized in attacking the disease. Whilst believing that irradiation is superior to other methods for certain types of bladder tumour I do not consider that, generally speaking, it offers exceptional benefits over the alternative procedures that are available and I employ diathermy, segmental resection and total cystectomy as well as irradiation alone or in combination according to the indications. Providing extirpation of the tumour is obtained the end-results seem not to be greatly influenced by the method whereby this is achieved; for the factors having the greatest bearing on the outcome of a bladder cancer are its degree of malignancy, the area of bladder wall that is involved and, in particular, the depth of penetration through the wall. Table I shows the

TABLE I.—METHODS EMPLOYED IN TREATMENT OF 171 NEW CASES OF BLADDER TUMOUR SEEN DURING 1950 AND 1951 *at Urological Department, Glasgow Royal Infirmary*

Treated by transurethral diathermy	65	
„ „ transvesical „	37	85
„ „ *transvesical irradiation*	32	
„ „ total cystectomy	11	
„ „ partial „	5	
„ „ palliative uretero-colic anastomosis	5	
No treatment	16	
	171	

methods of treatment employed on 171 new cases of bladder tumour seen at the Urological Department of the Glasgow Royal Infirmary in the last two years. Irradiation was used for 32 out of the 85 who had direct intervention on the bladder by open operation—that is 37·6%. Transurethral diathermy, which also includes resections, was the mode of treatment for the so-called benign papillomata though in some instances it was resorted to as a palliative for advanced lesions. The varieties I may select for treatment by irradiation are the solitary, sessile, broad-based papillary carcinoma occupying the lower zones of the bladder when the base of the tumour is not much greater than 5 cm. in diameter; or two or three contiguous tumours which are jointly of a similar size; or two separately placed tumours neither of which occupies an area greater than 5 cm. Flat non-papillary infiltrative growths or nodular tumours in corresponding areas of the bladder and again not exceeding 5 cm. in diameter are also irradiated. It will be apparent that I rely on the gross characters of a tumour and its location rather than on its histology as a guide to the mode of treatment. A provisional decision about the employment of irradiation is made following cystoscopy and bimanual examination but is not finally ratified until the growth is exposed at operation.

TECHNIQUE

(*a*) *Exposure and preparation of tumour-bearing area.*—The approach is by the extraperitoneal transvesical route. After opening the bladder by a vertical incision of adequate length the tumour-bearing area is fully exposed to view with the aid of a suitable self-retaining retractor. A papillary carcinoma that has not penetrated deeper than the mucosal layer can often be elevated upwards so as to create an artificial pedicle from the surrounding mucosa. It can then be completely removed by cutting across the root with a needle activated by the high frequency current. With tumours of deeper penetration into or beyond the submucosal or muscular layers such an elevation is not possible but the projecting portion can be reamed off with a loop electrode until the level of the bladder mucosa is reached; or alternatively the growth can be diathermied, the destroyed tissue scooped away and the process repeated until the bladder level is reached and no visible neoplastic tissue remains. To obtain the maximum benefit of irradiation the blood supply of the area should be conserved as far as possible.

In the case of bladder tumours radiotherapists seem undecided about the advisability or otherwise of withholding diathermy, a procedure which, of course, seals off the blood vessels. My practice in dealing with the tumour bed that is left after removing the bulk of the growth and to which the irradiation is to be given is to apply diathermy of an intensity sufficient to exert a destructive effect down to the muscular layer or even deeper. The diathermy is relied on to destroy the superficial surface of the tumour-bearing area. The radium or its emanation is then inserted at depth with the object of destroying islands of tumour tissue which may still persist. As the effect of irradiation decreases with distance this would appear to be a rational mode of procedure.

(*b*) *The irradiation.*—Until about two years ago I generally employed radium needles. One set had an active length of 1 cm. and contained 1·0 mg. of element. Another with an active length of 0·5 cm. contained 0·5 mg. of element. The objective was to deliver a homogeneous dose of 7,000 r over a period of 160 hours to the tumour-bearing area along with a zone of 1 cm. peripheral to it. Radon seeds each of 1 mc. strength were used when the area to be treated was less than 3 cm. in diameter as seeds seemed to permit of a more accurate distribution within those limited dimensions.

During the last two years, with the assurances given by radiotherapists that the tapering dose inevitably associated with radon is not less effective than the constant dose-rate of radium, my preference has been to use seeds in all cases because immediate closure of the bladder is possible following their insertion. In collaboration with Dr. Robert Morrison, Director of the Radiotherapy Department at the Glasgow Royal Infirmary, the strength of the seeds has been reduced to 0·6 mc. with, of course, a proportional increase in the total number used for each case. This increase in number permits of a more uniform and accurate control of the general dose level which is aimed to be at between 7,000 and 7,500 r. In the average case the area to be irradiated is under 5·5 cm. in diameter and two-thirds of the total seeds are placed round the periphery and the remaining third in an inner circle or ellipse. To illustrate an example of distribution let us take an area of 3 cm. in diameter. To give 7,500 r throughout the area would require a total dose of 10·9 mc. Using 0·6 mc. seeds, 18 would be required of which 12 would be placed at the periphery, less than 1 cm. from each other, and an inner circle or ellipse would be formed of the remaining 6. It should be noted that in any batch of seeds having a nominal value of 0·6 mc. there will be some variation in their strength, for each seed cannot be filled exactly to requirements. The average value of each seed will, however, be 0·6 mc. and the dosage will be accurate so long as the strong and weak are judiciously mixed.

Long-term Results of Irradiation

In 1948 I reviewed the results of 110 cases treated by radium in the decade 1934–43, that is, not less than five years had elapsed between the time of the review and the treatment of the last cases. The findings of that enquiry which are summarized in Tables II and III serve to show what can be expected from treatment by irradiation.

Table II.—Treated 1934–1943: Reviewed 1948

Total number of patients treated	110
Died from operation	11
Died of intercurrent disease: Cerebral hæmorrhage (2), cardiorenal failure (2), cancer of œsophagus, cancer of neck, cerebral tumour, epithelioma of palate, pulmonary tuberculosis, accident (2–5 years after treatment)	10
Used for this report	89
Died of bladder cancer (29 in 1st year, 9 in 2nd year, 7 in 3rd year, 4 in 4th year, 3 in 5th year)	52
Survived five years or longer	37

Table III.—Details of 37 Patients Who Survived Five Years or Longer

Died of recurrence in 6th year	1
Died of intercurrent disease: Cerebral tumour, 1 in 7th year; Cardiovascular disease, 2 in 8th year, 1 in 10th year, 1 in 11th year; Cerebral hæmorrhage, 1 in 10th year	
Abdominal ascites, 1 in 14th year	7
Alive and clinically free from cancer 6 to 11 years	29

The employment of radon seeds in place of the element is associated with a marked diminution in the incidence of gross post-operative urinary infection. This may in part be due to present-day routine use of chemotherapy but the closure of the bladder rendered possible because there is no need to remove seeds must also be credited with a share in the reduction of the infection and consequent diminished morbidity, particularly from pyelonephritis. Also of some importance and indicative of smooth convalescence is the ability of most of the patients to leave hospital in about two weeks whereas with radium needles and the need to establish suprapubic drainage, patients seldom left hospital within six weeks of operation. The following case history with the sequence of events subsequent to radium therapy four years ago in one patient is of interest.

In December 1947 a man of 51 years suffering from an invasive papillary transitional-cell carcinoma, located in the lower zone of the right postero-lateral walls and approximating on to the right ureteric orifice, had the tumour treated by interstitial irradiation. A severe radium reaction followed with a persistent encrustation on the tumour-bearing area which was not appreciably influenced by prolonged tidal irrigation with Suby's solution and other medication. After more than a year of frequency and dysuria, it was considered from the

cystoscopic appearances that tumour activity was still present and cystectomy was planned. In February 1949 the ureters were transplanted by the Coffey No. 1 technique. At that time the right renal pelvis and ureter were moderately dilated. A month later, before going ahead with the cystectomy, cystoscopy was repeated. All evidence of encrustation was seen to have disappeared and the irradiated site was now a smooth bloodless area. The cystectomy was not therefore proceeded with. Another cystoscopy three months later again confirmed the absence of any visible encrustation or neoplasm. In October 1950, i.e. two years and ten months after the irradiation, and one year nine months after the transplantation, the patient reported that he had passed blood *per urethram* and cystoscopy revealed a new growth in the middle zone of the posterior wall. The X-ray investigation also showed that he had formed a branching calculus in the dilated right renal pelvis. Cystectomy was now carried out and a few months later the right kidney was removed. To-day he remains well.

Because of the wide variation in the form, position, size, degree of penetration and histology presented by bladder tumours a comparison of the results that follow the different modes of treatment is a matter of intricacy and difficulty. It is difficult also to compare the results of the same methods when carried out by different surgeons because there is inevitably a lack of standardization of treatment for similar varieties of bladder cancer and individual surgeons incline to a particular method or combination of methods according to their own experiences. A large personal element, in consequence, enters into methods of treatment. What I consider a worth-while comparative assessment confirming the beneficial effects of irradiation is to be found in a monograph by Franksson who made a pathological and clinical study of 434 cases of bladder tumour treated in the Karolinska Hospital and Radium Institute, Stockholm. He compared the results of treatment by transvesical diathermy and by transvesical diathermy with radium in two groups of cases both having tumours of similar histological gradings. He showed that patients who had radium had not only a greater freedom from local recurrence but also exhibited a greater freedom from new growths in other areas of the bladder. Thus in 22 cases, in whom the tumour had not penetrated beyond the mucosa, treatment by transvesical diathermic excision was followed by new tumour formation in 90%, 9% of whom had recurrences at the original site; in 38 cases, again with tumours which had not penetrated beyond the mucosa, who had radium treatment as well as diathermy, there was new tumour formation in 58% with none of the recurrences at the original tumour site. He considered that the diminished tendency to new tumour formation in other areas following the radium was due to the effects of the irradiation on the collapsed walls of the bladder which came in close proximity to the radium. (*See* Franksson, C., 1950, *Acta chir. scand.*, Suppl. 151.)

This failure to prevent new tumour formation arising in areas away from the site of the original growth is one of the weaknesses of radium therapy even though there is evidence that it diminishes the incidence of these recurrences. Few would be prepared to advocate the wholesale employment of cystectomy as a prophylactic measure to cope with this particular problem. A disadvantage of a different nature associated with the employment of radon emanations is the need to obtain the seeds from a distant centre and the consequent necessity of giving notice of the estimated dose required with the date and time of operation. Seeds will not be available if their use has not been anticipated and conversely a change of procedure influenced by the operative findings or the need to postpone the operation will result in their wastage. The substitution of radioactive isotopes seems to promise a way towards a solution of some of these drawbacks.

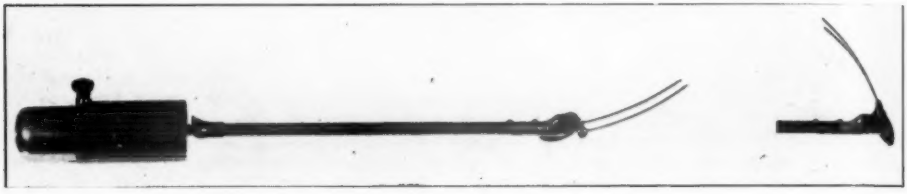
Mr. D. M. Wallace (Royal Cancer Hospital): There are two types of bladder tumour that have been treated by means of radioactive isotopes at the Royal Cancer Hospital. The first lesion is the medium or large-sized, papillary or solid carcinoma which has not, or has only just begun to infiltrate muscle, while the second lesion is the multiple, small, diffuse mucosal carcinomatosis, a lesion that has arisen over a large area of bladder mucosa but which has not yet begun to infiltrate. Isotopes have been used in these lesions purely as a method of applying gamma radiation to the tumour cells in adequate doses and with the minimal damage to normal tissue.

The follow-up in this series is short because the intracavitary method has been in use for just over two years and the interstitial wire method has been in use for a year. The results cannot be assessed as a long-term policy but the advantages and dangers of each method can be discussed in detail.

The solitary lesion, the so-called malignant papilloma, the pedunculated, papillary or solid transitional-cell carcinoma arising from an area of normal mucosa, which has not yet begun to infiltrate or where infiltration is limited to the inner layers of the bladder wall, can be treated by two methods. The smaller lesions, less than 3 cm. in diameter, can be treated by endoscopic resection followed by diathermy coagulation to the base so that complete destruction of the tumour is effected in one or two treatments. The larger lesions can also be treated by multiple diathermy coagulation but as one does not treat a carcinoma elsewhere by multiple, repeated sublethal irritations, it is probably better to excise the lesion transvesically and to implant the base with some form of radiation to cope with any infiltration of the muscle. To open the bladder for this type of lesion may result in tumour implantation in the wound but if certain precautions are taken, this risk is minimal. The technique adopted has been to open the bladder when it is full to prevent premature incision into the tumour. The bladder wall is then held up so that the tumour may be seen. A glass thistle funnel, slightly smaller than the tumour, is then fitted on to the end of the sucker tube and the tumour sucked into the funnel.

No instrument touches the tumour which is kept within the funnel by the maintained suction. The pedicle of the tumour is exposed with minimal amount of bleeding and in suitable cases can be clamped and cut with diathermy. It is possible to remove the tumour complete without risk of fragmentation or spilling malignant cells in the wound. Once it has been removed the problem of the tumour bed arises. As the effect of irradiation in the tumour bed is optimum when there is a healthy blood supply, where the tumour pedicle has been small enough to allow it to be clamped and oversewn, the source of radiation has been inserted without diathermy coagulation to the base. When the tumour has been a relatively sessile one or with a wide pedicle, the base has been extensively diathermied prior to the insertion of the source of radiation.

There are three methods of interstitial irradiation that can be used in the bladder wall. Radium or radon as described by Mr. Jacobs, tantalum wire which has been in use now for the last year, and radioactive gold seeds sheathed in a platinum cover, a technique which is still in the experimental stages. Radium has several advantages over radon but has one major disadvantage, its bulkiness and the lack of flexibility with the consequent need of a second intervention to remove the needles



A

FIG. 1A.—Modified boomerang needle holder fitted with paired needles.

B

FIG. 1B.—Needles flexed ready for insertion of wire.

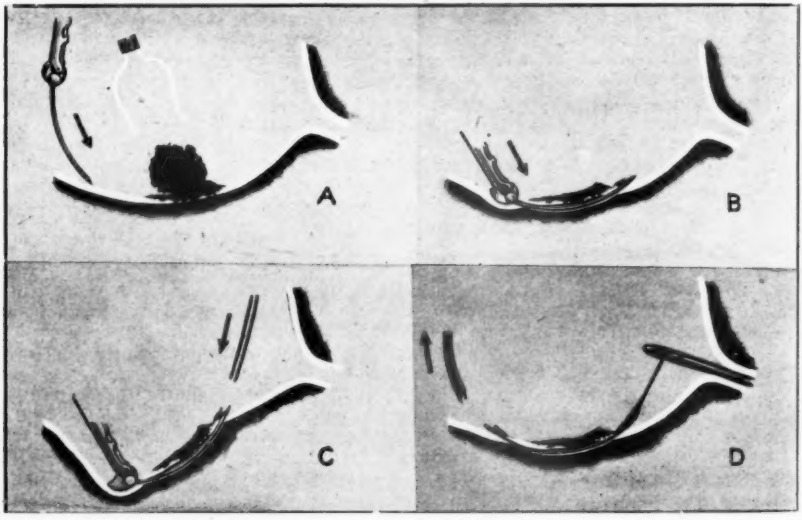


FIG. 2.—Diagram of method of insertion using paired needles and thistle funnel sucker.

or else the bladder must be left open. Radon seeds allow the bladder to be closed and they do not require to be removed subsequently but they too have certain disadvantages. They are not readily available and they require about a week for preparation. It is not certain that a good geometric implant will be obtained every time, seeds sometimes fall out and they can easily be inserted either farther apart or closer together than the 1 cm. spacing allowed. Even if inserted correctly the movements of the bladder wall may alter the shape of the implant. The seeds, once inserted, cannot be removed nor can the dose of irradiation be altered to compensate for any defect in the implant. Finally with the seeds remaining in situ, it may be difficult to detect a recurrence since there may be considerable induration surrounding the seeds.

Tantalum wire was first suggested by Mayneord as a possible flexible source of irradiation and was used by Ledlie, Lederman and Harmer for growths of the stomach, palate and tongue respectively. The wire can be irradiated in the atomic pile to any reasonable strength of activity required. It is suggested that wire of 1 mc. per centimetre is about the optimum strength for implantation. The wire is sheathed in platinum so that the beta radiation is filtered off.

The flexibility of this wire is comparable to that of domestic 10 amp. fuse wire. After irradiation, the wire has a half life of 120 days so that it can be kept for a considerable time at a strength of therapeutic value. At a nominal cost it can be reactivated by a second insertion into the atomic pile.

The insertion of tantalum wire is technically easier than radon seeds. Two hollow curved needles[1] mounted 1 cm. apart on a modified boomerang needle holder (Fig. 1) are inserted outside the periphery of the area to be treated and guided in the plane of the bladder muscle towards the internal meatus

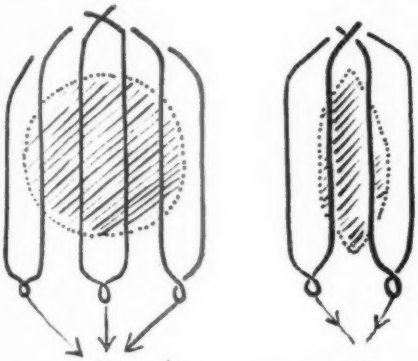


FIG. 3.—Diagram of idealized implant. (*a*) 4 cm. lesion. (*b*) 2 cm. lesion.

FIG. 4.

FIG. 5.

FIGS. 4 and 5.—Wires in situ in bladder. (Note free ends of wire are now not interlocked.)

to emerge on the opposite side of the tumour bed (Fig. 2). When correctly placed the needles are flexed so that the points present towards the operator. A hairpin of wire, one limb longer than the other and with a small loop in the centre is then threaded into the needles, which are then withdrawn so that the wires come to occupy their position in the plane of the bladder muscle. This method of arranging the wires can be seen in Fig. 3. The wires once they have been inserted act as splints to prevent the buckling up of the bladder muscle. The wires are tied by silk to a urethral catheter and the bladder closed in layers (Figs. 4, 5). When the amount of irradiation is adequate, the wires are

[1] Made by the Endoscopic Instrument Company, London.

removed by withdrawing the catheter down the urethra. As the wires are flexible this causes very little discomfort. With the present method of fixation, no wires have been left behind in the bladder although with a different method three wires did slip off. These wires were easily retrieved by means of grab forceps and a panendoscope. Apart from one death due to a cerebral hæmorrhage, all the cases treated are tumour free.

The multifocal superficial carcinomatosis of the bladder has been a surgical problem for which no single form of therapy has been found to be effective. Until more is known about the ætiology of this disease any treatment which effects complete tumour sterilization but which does not control the predisposition of the mucosa to undergo malignant change, and therefore the development of fresh primary tumours, can only be palliative. In an attempt to irradiate the whole of the bladder mucosa and yet to spare as much as possible of the bladder muscle and the perivesical tissues, the technique of intracavitary irradiation was introduced. The earlier work was done by means of either radium (Friedman) or solid radioactive cobalt (Low-Beer) in the centre of an air-filled balloon. This type of irradiation has two disadvantages: firstly the bladder muscle gets almost the same dose as the mucosa due to the relatively gradual falling off of dose with depth and secondly, unless the point of irradiation is placed and kept exactly in the centre of the balloon, one side of the bladder may receive a dangerously high dose while the opposite side may receive too little. A bag filled with a solution of a radioactive salt does not have this disadvantage and, using bromine, a high homogeneous irradiation for 5 mm. outside the surface of the bag and a steep falling off in the dose beyond this distance can be achieved. A bag filled with fluid provides a good method of intracavitary irradiation and is ideal for the treatment of a narrow zone of the whole of the bladder wall since the dose is uniform and the extravesical tissues receive little irradiation.

Once the patient has been selected as suitable, the method of treatment consists in the insertion of a modified Miller-Abbott tube into the bladder, in men through a perineal urethrostomy, in women through the urethra. The smallest bag compatible with safety was found to be too big for the average male urethra so that urethrostomy is performed as routine and after dilatation of the posterior urethra, the bag is inserted via a cannula. The cannula prevents the bag folding up in the urethra and minimizes operative trauma. When the bag has been inserted, the isotope solution is introduced by means of a pressure suction device so that the operators receive a minimal amount of irradiation. After about an hour the solution is removed and the bag withdrawn. This treatment is repeated at weekly intervals for three applications, each of which aims to administer 2,000 r gamma and 400 r beta radiation. Serial biopsies have shown a progressive tumour response and increase in the tumour bed reaction, and in one patient who died from a cerebral accident six weeks after treatment it was possible to demonstrate complete disappearance of the tumour with the exception of a few atypical cells in the extravesical lymphatics.

The immediate post-therapy period is usually uneventful—the women are continent within a few hours and the men leak only during micturition for about ten days after treatment. There has been no case of incontinence due to stretching of the sphincter nor has there been a fistula that persisted for longer than a fortnight after the last treatment. The results obtained in a series of 45 cases are based on a short follow-up, but they are instructive, inasmuch as they demonstrate that there are dangers and complications attendant on indiscriminate irradiation.

The cases can be considered in three groups, (1) those undertreated, who received less than 3,000 r at a single treatment, (2) the overtreated who were given 4,000 r at a single treatment, and (3) the most recent group who received 2,000 r on three occasions at weekly intervals.

3 cases died from carcinomatous deposits but one had a bladder that was tumour free shortly before his death.

6 cases have had total cystectomy as the lesion failed to respond.

2 cases died in uræmia from a small contracted bladder with hydro-ureters and hydronephroses. Another case has hydro-ureters but a normal blood urea and refuses transplant because his symptoms are minimal. Only 2 cases have had their ureters transplanted. All these 5 cases had complete tumour regression. They were all treated by a single application of 4,000 r.

4 cases had a minimal lesion after irradiation and these lesions were cautiously diathermied. They are now tumour free. There are 5 cases that have a lesion in their bladders that may be tumour or may be radionecrosis. These are being watched.

2 cases died from urinary sepsis, 1 was tumour free but the other had considerable residual tumour at post-mortem. In 1 woman a vesicovaginal fistula developed after a year, although her bladder was apparently tumour free. There was 1 death from cerebral hæmorrhage six weeks after treatment and this bladder was tumour free.

The remaining 18 cases are tumour free and have a useful bladder.

The bad results developed in the group of cases that were overtreated although it is a moot point whether complete tumour regression followed by a transplant is worse than a total cystectomy. The incomplete tumour sterilization occurred mainly in the group of undertreated cases; some were amenable to minimal diathermy but the majority have had a total cystectomy. The fractionated group, the most recent group of all, have none of them developed a systolic bladder and the tumour regression appears to be adequate. To achieve tumour sterilization in 60%, if it can be done without causing a

contracted bladder, will mean that intracavitary irradiation has a definite place in the treatment of bladder carcinoma.

In conclusion, the cases that are most suitable for this form of therapy are the multiple mucosal carcinomata where there is no abnormality in the pyelogram and where there is no abnormal thickening of the bladder wall on bimanual examination. High-grade and average-grade lesions respond better than the low-grade ones. Previous diathermy treatments appear to result in a greater incidence of incomplete tumour sterilization by comparison with untreated cases. As the treatment is not yet as certain as it should be, cases accepted for treatment by this method should be beyond diathermy control and suitable only for total cystectomy as an alternative.

Dr. R. J. Walton desired to fill in one or two small gaps left in Mr. Wallace's contribution. In treating a carcinoma of the bladder by external radiation the object was to deliver to the tumour and the tissue immediately surrounding it a dose of radiation sufficient to cause the tumour to regress and disappear while producing minimal permanent damage to normal tissue.

This immediately brought one face to face with perhaps the most important factor which might determine the suitability of a patient for treatment by this method, namely, tumour size. Experience had taught that a deep-seated tumour occupying a volume greater than 5 cm. in diameter would probably not be given a dose of 6,000 r in five to six weeks without the occurrence of excessive local and general reaction. Once a suitable tumour was selected it should be irradiated with the highest voltage obtainable. The higher the voltage the greater the penetration of the rays and consequently the less damage likely to be inflicted on the skin and superficial tissues for a given dose to the tumour. Suitable voltages were 250 kV, 400 kV, and 2 MeV, with the latter showing undeniable advantages in all respects. It should be noted that the biological effect of the rays was identical in each of the voltages within this range. Even at 2 MeV, it was necessary to apply the radiation by means of several fields or by a continuously moving field.

In this way each area of skin received radiation from one beam only, while all beams contributed to the dose delivered to the tumour. The position of the tumour was localized by radiographic means, using a contrast medium and applying the fields so that each would irradiate the whole of the tumour. This description applied to treatment undertaken with a view to cure, and reactions were to be expected. These, at 2 MeV, were mild, consisting of erythema of the skin, some frequency of micturition, and perhaps a few more stools than normal. Radiation sickness was usually absent. Such a favourable picture could hardly be expected at 400 kV and still less at 250 kV.

The use of external radiation for palliation was another problem entirely. Here the aim was to reduce symptoms without producing others. Hæmorrhage and pain due to nerve involvement yielded to an extent to make treatment worth while. For obstructive symptoms, he thought a transplant or endoscopic resection was preferable.

Results[1] of radical and palliative therapy are shown in the accompanying table.

RESULTS FOR PATIENTS TREATED BY EXTERNAL IRRADIATION

	Number of patients	Estimated survival rate (life table method)		
		6 months	1 year	2 years
Stages 2 and 3, Radical	53	85%	74%	66%
Stage 4, Palliative	18	Mean period of survival 4·8 months		

Mr. F. Masina: I should like to make a few remarks, not about treatment, but about the clinical information which is necessary in order to plan treatment in bladder tumours. In 1949 Dr. Cuthbert Dukes and I suggested four essential features in the clinical assessment of epithelial tumours of the bladder (*Brit. J. Urol.*, **21**, 273).

(1) Gross characters which are assessed by cystoscopy.

(2) Histology which is judged by perurethral biopsy.

(3) Extent of spread which is estimated by co-ordinating I.V.P. and bimanual examination together with the previous factors.

(4) Surroundings of the tumour.

Further experience has confirmed the importance of these features in assessment not only of bladder tumours, but of almost all bladder lesions.

I shall consider very briefly only one of these features, No. 4, "Surroundings of the tumour".

Sometimes a bladder with a papillary tumour is surrounded by apparently inflamed mucosa (colour photograph shown). Cystoscopically it may be difficult to assess this mucosal change without a careful consideration of the whole picture, such as the symptoms, examination of urine for infection, perurethral biopsy, and if necessary response to treatment for infection. Perurethral biopsy may clinch the diagnosis. The biopsy fragment may demonstrate the tumour, in which we are not interested at the

[1]See *Proc. R. Soc. Med.*, 1951, **44**, 943.

moment, and the adjacent mucosa and submucosa, in which we are interested. If the adjacent mucosa is examined more closely it will probably show another early malignant focus.

In passing I would just like to mention the submucosal changes of lymph follicle formation, and the very marked increase in vascularity as indicated by the well-formed blood vessels. Some people hold that these are changes due to bacterial infection, others say that they are the result of diathermy treatment. Both these statements are inaccurate. These are submucosal changes often associated with tumour formation. Such altered mucosa is destined to form new tumours. The conclusion is this, that if a tumour is surrounded by diffusely red and apparently inflamed mucosa these changes are pre-malignant and malignant till proved otherwise. It is hardly necessary for me to enlarge on the significance of this factor in planning treatment.

There are, of course, several other types of mucosal changes, but here I shall refer to only one common erroneous teaching and observation. At cystoscopy one is frequently shown a bladder tumour with adjacent mucosal changes which are labelled as œdema. Nearly always these changes are early stages of tumour formation and not œdema for if a section is taken from the so-called œdematous area it frequently shows an early frond and sometimes adjacent to it hyperplasia of the mucosal cells.

Though I have merely touched the fringe of this interesting subject of mucosal changes, I must stress the difficulties of assessing them; these changes are as variable as the tumours themselves. With some mucosal changes, as with some tumours, a patient can live a long, peaceful, and symbiotic existence. Other mucosal changes are only the earliest phase of the most destructive tumour.

In conclusion may I remind you that there is such a factor as mucosal change surrounding a tumour, and it is wise to plan treatment only after assessing and correlating these changes in conjunction with gross characters, histology, and extent of spread.

There is just one other point which I wish to mention: Many surgeons have a tendency to open the bladder "to look and see". The cystoscope is the best instrument for looking and seeing and not a cystotomy, particularly as sometimes it is extremely difficult to assess these changes in a collapsed bladder. If the first cystoscopy is unsuccessful it should be repeated a second time, and if the second is unsuccessful it should be repeated a third time. On very rare occasions indeed it may be necessary to perform a cystotomy to establish the diagnosis, but otherwise a bladder should only be opened to carry out a previously planned treatment after the establishment of a complete diagnosis.

(These remarks were illustrated with nine slides.)

Mr. D. S. Poole-Wilson said that the cases of carcinoma of the bladder received at the Christie Hospital and Holt Radium Institute, Manchester, like those at the Royal Cancer Hospital, were a selected group. Amongst them was a high proportion of inoperable tumours, which made one realize the limitations of the present form of treatment. He showed a slide (*see* Table I) giving statistics of all the cases of malignant tumours of the bladder coming under his care at the Christie Hospital during the years 1946 and 1947. Of 138 patients only 48 (35%) were suitable for any form of open operation. It was felt that perhaps too conservative a selection had been made and in the following year the field of operative treatment was extended by carrying out open diathermy destruction and the insertion of radon seeds on more deeply infiltrating tumours, which would previously have been rejected for this form of therapy. Even so of 93 cases only 51 (55%) could be considered in any way suitable for open operation. It therefore appeared that at the Christie Hospital very nearly 50% of patients with malignant vesical tumours were beyond any operative curative treatment and only came into the treatable category as subjects for deep X-ray therapy.

TABLE I.—METHOD OF TREATMENT IN 138 CASES OF CARCINOMA OF THE BLADDER, 1946 AND 1947.

1.	Open diathermy and radon seed implant ..		43
	Alive (January 1950)	33	
	Dead (January 1950)	10	
2.	Radical X-ray therapy		43
	Alive (January 1950)	21	
	Dead (January 1950)	22	
3.	Palliative X-ray therapy		27
	Alive (January 1950)	1	
	Dead (January 1950)	26	
4.	Other surgical procedures		5
	Alive (January 1950)	2	
	Dead (January 1950)	3	
5.	Carcinoma too advanced for treatment ..		20

With regard to the open operative treatment employed at the Christie Hospital partial cystectomy had been almost entirely superseded by open diathermy removal of the tumour and the insertion of radon seeds, to a dosage of 7,000 r, into its base and a surrounding free margin of 1 cm. of bladder wall. The seeds were implanted about 0·5 cm. deep into the tissues thus ensuring that a layer of tissue. 1 cm. deep and surrounding the whole of the base of the tumour, received a tumour-lethal dose of

radiation. The area of really effective radiation was therefore not large. In suitable cases the treatment had been extremely successful. Total cystectomy was now carried out only in a few very selected cases.

Deep X-ray therapy was the only form of treatment for the inoperable cases; he himself felt that it had a large field of usefulness. At the Christie Hospital they had been using a 500 kV machine with beam direction. There seemed no doubt that the higher voltage machines, although not increasing the volume of adequately irradiated tissue in the pelvis, made the treatment easier for the patient.

With regard to tantalum wire as a substitute for radon seeds, time alone would show which was the better. In respect of intracavitary radiation of the bladder it seemed possible that treatment from a central source might prove as effective and easier of management than the use of radioactive isotope solutions.

Mr. J. C. Anderson (Sheffield) believed that total cystectomy had no place whatever in the treatment of frank malignant disease of the bladder. Over a period of eighteen months from towards the end of 1948 and on into 1950, he carried out 11 total cystectomies for carcinoma. Many of these were in favourable cases, but of these patients only 1 was alive to-day. 4 had survived for two to three years, but 3 died of local recurrence or more distant metastases within a year. He abandoned the operation and had subsequently treated such cases either by partial cystectomy combined with some form of radiation or by radiation alone, and he was convinced that the results were better, although he could not produce any statistical evidence to that effect.

After total cystectomy the pelvic tissues were laid open to extension of the disease and it was impossible to give accurate prophylactic radiation. After the local operation there was no such opening up of tissue planes and accurate adequate irradiation could be applied immediately. In his opinion this accounted for the better results.

They were fortunate in Sheffield in having highly efficient apparatus for the purpose, and he had seen the most dramatic results follow in the treatment of the frank type of carcinoma. Again he spoke without any figures but he thought that the treatment of the multiple villous type of lesion by high voltage irradiation was disappointing and he believed that in many instances tumours of this kind had not been cured by irradiation. Total cystectomy might have a place in that type of lesion.

Mr. E. W. Riches, in replying on the discussion, said Mr. Jacobs and the Glasgow school had produced better results from radium treatment than anybody else, but radium did lead to a very unpleasant cystitis which lasted for as long as nine months. Eventually, if the patient could survive this—and many did—he might be cured. In the case of radon seeds this did not apply. One could close the bladder and drain by catheter, and the patient was ready to go out in from ten to fourteen days, and usually, if the dose had been correct, he did so after no more than temporary cystitis.

The spacing of the seeds was very difficult. In many cases it was almost impossible to put them on a prearranged pattern which had been planned with the radiotherapist. From the point of view of radiation of that type the tantalum wires which Mr. Wallace had shown might certainly have a future. They were convenient in many ways and spacing would be more accurate than with radon seeds. Tantalum had a half life of four months, so that a certain amount of it could be kept in stock, which was an advantage.

As to malignancy of the papillary type, there were many ways of curing it. Both Dr. Walton and Mr. Anderson had had the advantage of using a 2 MeV unit. He had seen some of their results and they were a tremendous advance on the results which had been obtained with machines having a lower voltage. The Sheffield results seemed to be quite remarkable, so that he was not surprised to hear that the wearisome operation of total cystectomy had been given up.

If Mr. Anderson in mentioning "frank carcinoma" was referring to the solid ulcerative type of carcinoma which was deeply penetrating he would agree with him. One was no more likely to cure that by total than by partial cystectomy, and 2 cases discussed in his Opening Paper were an illustration of that fact (*See* Figs. 3 and 4). They had not at present got a cure whether by surgery or irradiation or a combination of the two.

The work Mr. Masina had done on this subject had stimulated all their scientific interest. Mucosal changes around the tumour were most important; the whole plan of treatment might depend on whether the tumour was really localized or whether there was a spread beyond it.

Cystoscopy might be difficult but they must take into account the patches of cystitis, the trabeculations and the nodular elevations that were seen in other parts of the bladder. The question was whether to start by treating the whole bladder or by treating the tumour. Here he referred to the very extensive destruction carried out under Mr. Poole-Wilson's technique for the putting in of radon seeds. This worker had given up partial cystectomy and tended to do fewer total cystectomies, and it would be of interest to learn the ultimate results of treatment with radon.

The method of treatment depended very much on how long the condition had been in existence, in other words, the history was more important than the grading. But a table of survival of all cases according to grade showed that in grade I 55% survived up to fifteen years. Grades II and III in their results were fairly close to each other, and that was one of the reasons why he had suggested that if

TABLE VII.—SURVIVAL BY GRADES FROM THE TIME OF SEEKING TREATMENT

Grade	Years survived				
	One	Three	Five	Ten	Fifteen
I	66%	53%	47%	33%	36%
	61/92	33/62	22/47	6/18	4/11
II	40%	33%	30%	20%	11%
	24/59	16/48	10/33	3/15	1/9
III	44%	33%	41%	37%	0
	33/75	18/54	16/39	6/16	0/5

44 cases were ungraded.

figures of survival by grades were taken, a low grade (grade I) and a high grade (grades II and III) might be sufficient for the purpose. Certainly this was borne out by the survivals for one year and for three years, but at fifteen years, while there was a survival of 11% of the cases in grade II, there were no survivals in grade III. (Table VII).

Section of Surgery

President—DAVID H. PATEY, M.S., F.R.C.S.

[*February* 6, 1952]

The following specimens were shown:

True Pancreatic Cyst.—Mr. CLIVE BUTLER.

Large Cystadenoma of the Pancreas.—Mr. A. ELLIOT-SMITH.

Colloid Carcinoma of the Pancreas.—Mr. E. G. MUIR.

Scirrhous Carcinoma of the Stomach—Hour-glass Deformity, in a Male of 49.—Mr. HENRY THOMPSON.

Three Cases of Unusual Gastro-intestinal Hæmorrhage: (1) Fibro-leio-myoma of Upper Jejunum. (2) Adenoma of Stomach. (3) Carcinoma of Pancreas.—Mr. W. W. DAVEY.

Chronic Intussusception Due to Hæmangioma of the Cæcum in a Child Aged 2 Years.—Mr. R. E. HORTON.

Intussusception Due to Inverted Meckel's Diverticulum with Peptic Ulcer.—Mr. LAUGHTON LEASK.

Stricture of the Ascending Colon the lumen of which measured 0·3 cm. only, probably tuberculous in origin although now quite quiescent and causing no symptoms except when plum stones lying as foreign bodies in the cæcum became impacted in the lumen. 27 plum stones found with radiological evidence of their being there at least three years, and circumstantial evidence to suggest that the time was at least fifty years.—Mr. BRIAN TRUSCOTT.

Lymphadenoid Goitre in a Female aged 82.—Mr. A. S. TILL.

Pulmonary Cavernous Arteriovenous Fistula.—Mr. ALEXANDER GRAHAM (for Mr. R. C. BROCK).

Portal Vein Compression due to Hypernephroma with Cirsoid Arteriovenous Fistula in Right Kidney.—Mr. R. B. MCGRIGOR (for Mr. ALAN HUNT).

Section of Odontology

President—R. A. Broderick, D.S.O., M.D.S.Birm., F.D.S., M.B., Ch.B.Birm.

[*October* 22, 1951]

"Ne Sutor Ultra Crepidam" [*Abstract*]

PRESIDENT'S ADDRESS

By R. A. Broderick, D.S.O., M.D.S.Birm., F.D.S., M.B., Ch.B.Birm.

In the course of an Address on the development of dental treatment in hospitals and the present responsibilities of Dental Surgeons attached to General Hospitals, the President discussed the following cases:

Case I.—Dentigerous Cyst of Maxilla and Cyst of Mandible

Radiographs showed two large cysts on the left side, a maxillary dentigerous cyst and a mandibular cyst. The patient's mental calibre was poor and his physical condition not good. On this account the maxillary cyst was first operated upon by an oral approach, the cyst and antrum being thrown together, drained into the nose, and the oral incision closed with sutures. The mouth healed normally but the patient developed bronchopneumonia and a complete left sciatic paralysis. The latter was probably due to injury to the nerve by a penicillin injection, a possible accident of which we must always be aware. Eight months later the mandibular cyst was treated by enucleation and packing with bipp. After fourteen days an obturator was constructed, gradually reduced in size and later replaced by a denture.

Case II.—Calcified Cyst

The patient complained of pain in $\lfloor\overline{7}$. With the help of an indifferent radiograph a dentist attempted to extract this tooth under mandibular block anæsthesia. While employing a dental elevator, a loud crack suggested a fracture of the jaw. The case was referred to hospital where an extra-oral radiograph revealed a large radio-opaque mass partially filling a radiolucent area of definite outline in the ramus of the mandible behind $\lfloor\overline{7}$. The mandible was fractured just posterior to the angle (Fig. 1). Under general anæsthesia the mass was dissected out, the cavity packed and the fracture immobilized by inter-dental wiring. Healing was uneventful. The pathological report was inconclusive, a partially calcified cyst being more probable than an odontome.

Fig. 1 (*Case II*).

Fig. 1 (*Case II*).—Calcified cyst in lower third molar region, showing fracture at angle of mandible.

FIG. 2 (*Case III*).

Case III.—Compound Composite Odontome

A boy of 15 presented with a steadily enlarging swelling of the left mandible, becoming large enough to interfere with mastication. The differential diagnosis included adamantinoma, sarcoma, odontome or osteitis fibrosa. After the usual precautions the mandible was excised from the left canine to the condyle. Again this is a rare pathological specimen, the most likely diagnosis being a unilateral dysplasia of bone associated with an odontome (Fig. 2).

FIG. 2 (*Case III*).—Unilateral dysplasia associated with an odontome. Section from body of mandible.

Case IV.—Erythrædema (Pink Disease)

A child of 18 months was admitted to hospital with ulceration of the gums of such severity that several teeth had dropped out (Fig. 3). In association with the late Sir Leonard Parsons I have seen many such cases of pink disease, one of which died of cancrum oris, and I consider the mouth symptoms important. There is no specific treatment and I have found penicillin of little value for the mouth lesions. Arsenic preparations, gentian violet or hypochlorites may be tried but the treatment is mainly symptomatic. The ulceration heals as the general condition improves and the permanent dentition is not affected.

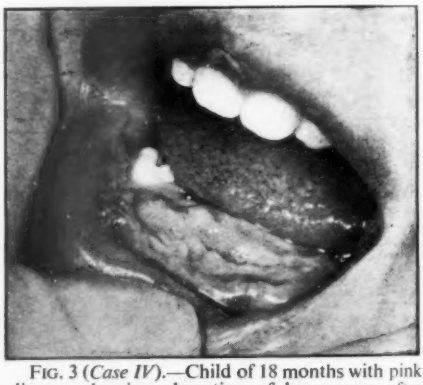


FIG. 3 (*Case IV*).—Child of 18 months with pink disease, showing ulceration of lower gum after loss of lower incisors.

FIG. 4 (*Case V*).—Unilateral lymphatic enlargement, showing old scars of face and overgrowth of tissue.

Case V.—Unilateral Lymphatic Enlargement

This case presented grotesque asymmetry of the face and jaws, due to overgrowth and œdema (Fig. 4). There were two large scars running from the ear to the chin, one above and one below the mandibular line, but no history could be obtained, the child being an orphan. The jaw was much enlarged and the teeth almost hidden by overgrowth of gum. On account of interference with articulation and mastication, extraction of teeth and alveolectomy was performed on the affected side. There was little differentiation between gum and bone and little bleeding, the tissues cutting like cheese and exuding a slimy blood-stained fluid. Healing was uneventful. It is probable that the two large scars had resulted in destruction and blocking of the lymphatic system with resulting hemihypertrophy.

Case VI.—Mixed Salivary Tumour of Palate

A patient was referred with a diagnosis of palatal abscess, there being swelling at the junction of the hard and soft palate. The physical signs did not confirm this and a provisional diagnosis of mixed tumour (salivary gland type) was made. The tumour shelled out easily and microscopy confirmed this diagnosis.

Subsequently all "lumps" which I removed from the mouth, irrespective of size and position, were examined histologically and more than 50% gave a similar report. I believe that a large number of these small "lumps" contain salivary gland tissue and therefore should be removed lest undesirable characteristics develop. When small the operation is simple—two curved incisions, a clean dissection and two stitches—and this may save a much larger operation later.

[*January* 28, 1952]

Foreign Body Reactions in the Oral Tissues

By R. B. Lucas, M.D., M.R.C.P., D.P.H.

Foreign body reactions occur in response to the presence in the tissues of particles or crystals which are not readily absorbable. Though these bodies may be of quite diverse nature the reactions occasioned by them all show certain common features, and though these reactions occur quite frequently in the body in general, some of them have been but infrequently described in the oral tissues. From the point of view of both the oral diagnostician and the pathologist who examines his biopsy material, therefore, it seems pertinent to draw attention to a class of lesion regarded as unusual in the mouth.

Foreign bodies may be classified as shown in Table I, and though not all these agents cause lesions in the oral tissues representatives from each main class can be shown to do so.

Micro-organisms which excite foreign body reactions include those which cause the chronic granulomata—tuberculosis, syphilis, actinomycosis, leprosy. Histologically, these diseases show the essential features of foreign body reactions—the accumulation of chronic inflammatory cells, prominent among which are large histiocytes or "endothelioid" cells, and the formation of giant cells. In these granulomata the foreign bodies—the causal organisms—can be demonstrated by appropriate staining methods.

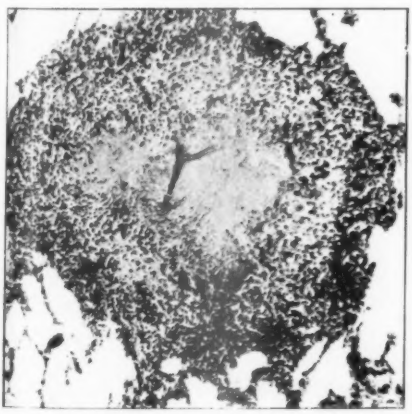


Fig. 1.—A tubercle follicle in the lung, showing a central area of necrosis surrounded by a zone of endothelioid cells, with occasional giant cells, and an outer layer of lymphocytes. × 68.

Fig. 1 shows a tubercle follicle, illustrating the essential features of the foreign body reaction. Characteristically, this lesion is compact and follicular and shows in its central part an area of necrosis or caseation, due partly to the toxins of the tubercle bacilli and partly to anoxæmia, since the tubercle follicle is avascular. Surrounding the central area of caseation is the zone of reaction. Here there are numerous endothelioid cells, macrophages which represent the tissues' efforts at cellular defence. Some of these macrophages fuse to form giant cells. The zone of macrophages is surrounded by a layer of lymphocytes.

Sarcoidosis has been included here with the specific granulomata; though the cause of this disease is as yet unknown many authorities consider it to be a type of tuberculosis. Oral lesions in sarcoidosis appear to be rare—only 3 cases are recorded in the dental literature. Schroff (1942) has described a lesion in the cheek, Poe (1943) reported a case with involvement of the mandible, and in Read and Campbell's (1944) case the lesion was situated in the maxillary buccal sulcus. The following case, in which a gingival lesion showing the histological appearances of sarcoidosis was present, is therefore of interest.

Case I.—The patient was a boy of 16, first referred to hospital three years ago on account of gingival hyperplasia found on routine examination by the School Dental Officer. He had not complained himself,

and his general health was good. On examination general proliferation of the gingivæ was found. This was present in all areas, but was especially marked in the lower incisor region. There was no evidence of active inflammation.

A biopsy was performed, and the microscopic appearances were as shown in Figs. 2 and 3. Fig. 2 is a low-power view, and shows that the normal gingival connective tissue is replaced by a massive cellular infiltration with a distinct follicular arrangement. Examination under a higher power (Fig. 3) shows these follicles to consist of quite large cells, similar to the endothelioid cells of the tubercle follicle. Large giant cells are prominent and the whole follicle is surrounded by a zone of lymphocytes, amongst which are a few plasma cells. There is no caseation and no tubercle bacilli were found in specially stained sections. The lesion thus conforms histologically to sarcoidosis. No other evidence of this disease was found in a general examination. No specific treatment was carried out, and shortly after being discharged from hospital the patient joined the Army. He reported by letter recently, to say that his gingival condition had not altered and that he was in good general health.

Fungi form another class of micro-organisms which cause foreign body reactions. Fungal infections, apart from ringworm, moniliasis and to a lesser extent actinomycosis, are rare in this country though in recent years an increasing number of cases have been reported. Most of these diseases are systemic, but lesions involving the mucous membranes also occur. In the conditions caused by the fungi noted in Table I, oral lesions have been reported. Occasionally such oral lesions constitute an early manifesta-

TABLE I

I. LIVING ORGANISMS:
- 1. *Bacteria*:
  - (i) *M. tuberculosis*
  - (ii) *M. lepræ*
  - (iii) *T. pallidum*
  - [(iv) Sarcoidosis]
- 2. *Fungi:*
  - (i) *Actinomyces bovis*
  - (ii) *Blastomyces dermatitidis*
  - (iii) *Coccidioides immitis*
  - (iv) *Geotrichum*
  - (v) *Cryptococcus neoformans*
  - (vi) *Monilia albicans*
  - (vii) *Histoplasma capsulatum*
  - (viii) *Sporotrichum schenckí*
- 3. *Protozoa*
- 4. *Plant forms*

II. LIPOID DROPLETS AND PARTICULATE MATTER:
- 1. *Introduced from without*:
  - (i) Suture materials
  - (ii) Cotton-wool
  - (iii) Asbestos
  - (iv) Amalgam
  - (v) Silica
  - (vi) Fat
- 2. *Arising within the body*:
  - (i) Fat
  - (ii) Keratin

tion of disease, so that the dental surgeon may be the first to see the case. Oral lesions take the form of patches, as in thrush, or ulcerations in various parts of the oral cavity. These latter are not characteristic in appearance so that the ultimate diagnosis depends on biopsy. The histological lesions produced by all varieties of fungi are fairly similar; they consist of an inflammatory and foreign body reaction in which giant cells are often prominent and the causal organism can always be found, except in the case of sporotrichosis, where cultures have to be made. Sections stained by Gram's method should be examined in suspected fungal lesions, as well as the routine hæmatoxylin and eosin preparations, since in the latter the fungal forms may be mistaken for lymphocytes or other cells.

Protozoa as causal agents in foreign body reactions require little consideration in the case of the oral region, since the only protozoon found in the mouth, *Entamœba gingivalis*, is non-pathogenic. The dental surgeon may, however, note the scars of dermal leishmaniasis, quite often seen on the cheeks of Asiatic patients.

Foreign body reactions caused by plant elements may also be mentioned. Lycopodium spores have been used as surgical glove powder and hence have gained access to operation sites and caused foreign body reactions, while the spines of certain species of cactus, and wood splinters, have caused similar lesions.

The second class of agents causing foreign body reactions comprises lipoid droplets and crystals, and particles of various types. These agents are usually introduced into the tissues from without, but some substances also arise within the body, as a result of pathological processes, and are then treated by the tissues as foreign matter.

Substances very commonly introduced into the tissues from without are suture materials, and a foreign body reaction accompanies absorption of catgut, nylon, &c. Similarly, cotton-wool may become incorporated into operation wounds and provoke a reaction. Another substance which may be introduced into the tissues from without is fat, in the form of droplets. This may occur with the prolonged use of oily nasal sprays: some of the droplets gain access to the lungs, where a granulomatous condition and foreign body reaction is produced—lipoid pneumonia. This condition

FIG. 2 (*Case I*).—Subepithelial connective tissue is replaced by dense cellular infiltration arranged in a follicular manner. × 80.

FIG. 3.—H.P. view from area in Fig. 2. The follicles consist of endotheloid cells. Giant cells are present, and there are some lymphocytes around the periphery of the follicles. × 160.

FIG. 4.—Paraffinoma. The empty spaces contained paraffin in vivo. Heavy chronic inflammatory infiltration and foreign body giant cells are present. × 90.

FIG. 5. (*Case II*).—Follicular aggregations of cells are present in the connective tissue. × 40.

FIG. 6.—H.P. view of one of the follicles. It consists of large mononuclear and giant cells. Lymphocytes also present. × 160.

FIG. 7 (*Case II*).—Same follicle as Fig. 6 photographed by polarized light, showing numerous doubly refractile particles. × 160.

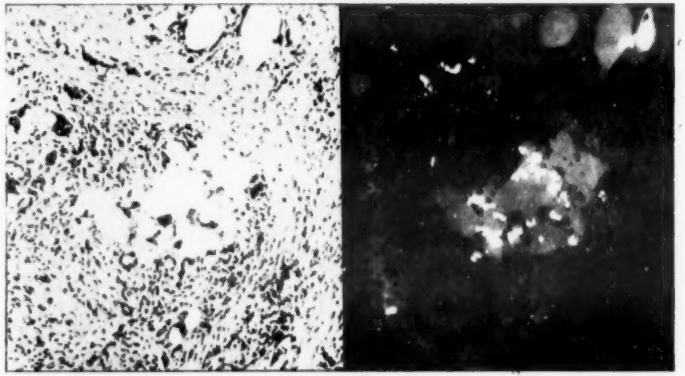


FIG. 8 (*Case IV*).—On left, granulation tissue showing chronic inflammatory infiltration and numerous giant cells. × 52. On right, the same field, under polarized light. Many doubly refractile particles are seen. × 52.

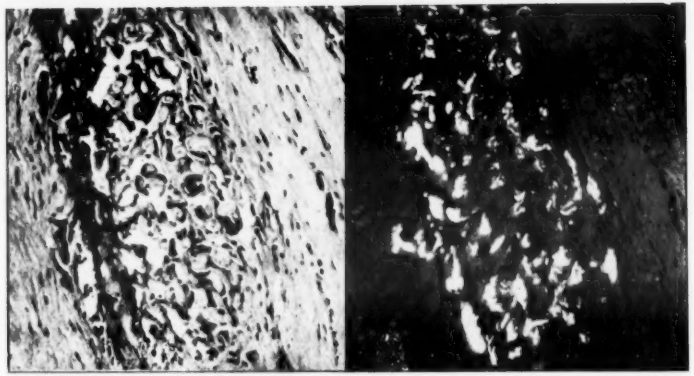


FIG. 9 (*Case IV*).—On left, a large aggregation of mononuclears and giant cells. × 134. On right, the same field under polarized light. × 134.

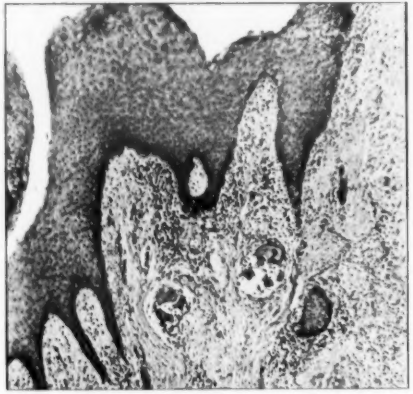


FIG. 10 (*Case IV*).—The surface epithelium is slightly thickened and small isolated areas of epithelium are present in the corium. Chronic inflammatory infiltration and large giant cells are present. × 40.

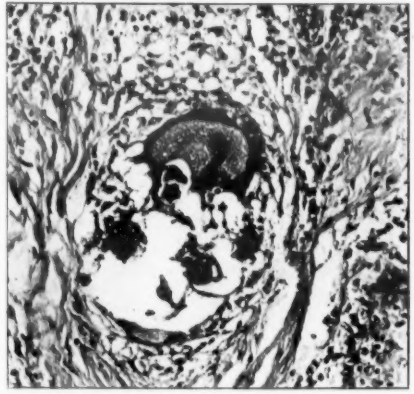


FIG. 11.—Detail from Fig. 10. A large giant cell is seen, in relation to small darkly staining masses. × 160.

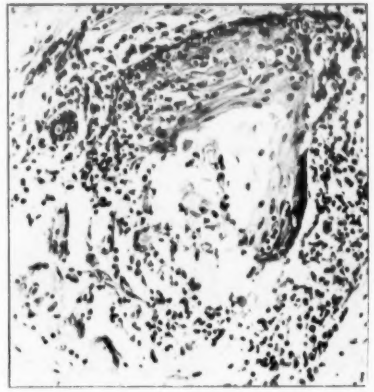


FIG. 12 (*Case IV*).—An islet of epithelium which has liberated keratin into the connective tissues, causing a foreign body reaction. × 142.

is also seen in infants taking cod-liver oil, particularly weakly infants who have some defect such as cleft palate which interferes with the mechanism of swallowing. Apart from the accidental introduction of fat into the tissues its deliberate introduction may also occur, as for instance in that condition which may be seen by the oral surgeon, paraffinoma. Here paraffin wax is injected into the subcutaneous tissues, usually in elderly women, for the purpose of removing wrinkles from the cheeks and restoring the contours of youth. The result is a marked chronic inflammatory and foreign body reaction (Fig. 4).

Other foreign bodies which may be introduced into the tissues include amalgam and silica. Foreign body reactions due to amalgam have been described by Orban (1946), while those due to silica have occasioned a considerable amount of interest in recent years, mainly as the talc granulomata reported from the field of general surgery, talc being a complex magnesium silicate.

The first case of a foreign body reaction due to silica was reported by Shattock (1917). The patient was a man who had cut his lip in a road accident. The wound healed in due course, but after an interval of some years a hard nodule appeared at the site of the old injury. This was excised and on section was found to consist of a foreign body reaction in relation to certain particles. These particles were insoluble in fat solvents or in nitric acid, were doubly refractile and had the appearance of silica crystals. Shattock concluded that these silica crystals had gained access to the wound from road dust. More recently, silica has been implicated in the causation of granulomatous lesions following abdominal operations (Roberts, 1947). In these cases it has been considered that the talc used as glove powder has been responsible.

The first gingival lesions due to silica have recently been reported by Kramer (1952). In a careful study of a series of gingivectomy specimens he noted the presence, in 6 cases, of foreign body reactions in relation to particles possessing the properties of silica. A further 2 cases are reported here.

Case II.—A woman of 53 reported to hospital for routine dental treatment. Several carious lesions were present and also chronic marginal gingivitis. Gingivectomy was performed on three occasions. Microscopic examination showed the usual histological changes of chronic gingivitis, but more striking was the presence of cellular aggregations quite deeply placed in the subepithelial connective tissue. One of these lesions is shown in Fig. 5, and is seen to consist of a compact focal accumulation of fairly large cells. There is very little inflammatory infiltration in the surrounding tissues, though close around the lesion itself there is an accumulation of lymphocytes. Examination of a lesion under a higher power (Fig. 6) shows it to be composed of large histiocytes and giant cells of the foreign body type, together with lymphocytes and an occasional plasma cell. No foreign bodies are seen, there is no caseation or necrosis, and no tubercle bacilli were seen in appropriately stained sections. On examination with polarized light, however, doubly refractile particles, situated to a large extent within the giant cells, become apparent (Fig. 7). These particles are not affected by treatment with fat solvents nor are they dissolved by nitric acid.

Case III.—A woman now aged 32 reported to hospital four years ago with bleeding gums, which she had then had for two or three years. She was found to have generalized subgingival calculus and a certain amount of supragingival calculus. She was treated by scaling and polishing, packing with zinc oxide and oil of cloves impregnated in cotton-wool, and tannic acid and glycerin were used in gingival massage. Eighteen months later the condition recurred and similar treatment was given, with temporarily satisfactory results. Two years later there was recurrence, and after further conservative treatment gingivectomy was performed. Microscopical examination of the tissue removed showed similar appearances to those found in the last case.

Kramer (1952) has pointed out that the significance of these lesions as a factor in periodontal disease is as yet uncertain, and there is no definite evidence as to how these doubly refractile particles have gained access to the tissues in most of the cases reported. However, in Case II, there is a history of manipulation of the gingivæ, including the insertion of packs, over a number of years, and it is possible that a pack or packs had become contaminated with silicates.

Another case of foreign body reaction due to doubly refractile particles is of interest because the foreign material appears to have gained access to the tissues by way of an operation wound. In this respect, therefore, the case is analogous to those of the abdominal granulomata mentioned earlier.

Case IV.—The patient was a girl of 15 who came to hospital with extensive caries in both upper central incisors. After dressings and cavity preparations an inlay was fitted to the upper left central incisor, but five months later an acute abscess formed over this tooth, which pointed and drained. Five days later the root canal was opened and drained for seven days. Thereafter it was treated with tricresol and iodoform, and prepared for root filling. During the course of this preparation, however, swelling and pain occurred over the upper right central incisor. It proved very difficult to get either canal into a fit state for permanent filling, and ultimately apicectomy was performed on the upper left central incisor. Two months later the patient fractured the crown of the upper right central incisor, when it was decided to extract both incisors. A month later the patient complained of pain in the upper left central incisor region. A flap was opened up and granulation tissue removed from the socket. The pain still continued, however, despite electrical treatment given in the course of the next four months. The labial mucoperiosteum from canine to canine was therefore reflected, and a cyst-like cavity filled with caseous-appearing material was found. Progress following this operation was satisfactory for about a month, when the pain returned. Three more operations of the same type were performed over the course of the next six months for recurrence of pain, and on each occasion, material resembling granulation tissue was removed.

FIG. 12 (Case IV).—An islet of epithelium which has liberated keratin into the connective tissues, causing a foreign body reaction. × 142.

FIG. 11.—Detail from Fig. 10. A large giant cell is seen, in relation to small darkly staining masses. × 160.

FIG. 10 (Case IV).—The upper epithelium is slightly thickened and small islets of epithelium are seen in the corium. Chronic inflammatory infiltration and large giant cells are present. × 40.

Histological examination of all specimens showed similar features (Figs. 8 and 9). The biopsy material consisted of connective tissue heavily infiltrated with chronic inflammatory cells, this infiltration extending up to the muscular attachments and penetrating between the fibres and destroying them. Numerous foci of foreign body giant cells and large mononuclear cells were present, in relation to doubly refractile particles.

How these particles gained access to the tissues is a matter of conjecture. Gutta-percha contains silicates, apparently in varying amount according to the batch. As this substance was used during the course of treatment, and also zinc oxide, it seemed possible that these materials might have contained silicates in undue amount or as a contamination. Samples in current use in the hospital were therefore investigated. Aqueous suspensions of ground-up material were injected subcutaneously and intramuscularly into guinea-pigs, which were then killed at intervals, up to three months. 8 animals were used, 4 for each substance. In no instance was any comparable lesion produced. This negative experiment, of course, only shows that the materials actually used in the animals produced no lesion. It is possible that accidental contamination of the materials used on the patient occurred some time during treatment. This would appear to be the likeliest explanation.

With regard to foreign bodies arising within the tissues themselves, these include lipoid substances and keratin. These substances are, of course, normal constituents of normal tissues—when they remain in their proper places. But when cellular degeneration takes place lipoids may be precipitated as crystals, or appear as free droplets, and in the case of keratin this substance may be formed in sites other than the free surfaces of epithelia. In such circumstances—the appearance of normal tissue constituents in abnormal physical form or in abnormal sites—we find that these constituents are treated by the tissues as foreign bodies.

For example, in the dental cyst necrosis of cells leads to the liberation of fat which is deposited in the form of cholesterol crystals. Sometimes these crystals are precipitated within the cavity of the cyst, in which case they are separated from the connective tissue of the cyst wall by the epithelial lining. In such a case there is no reaction to the crystals because the epithelial lining effectively shuts them off from the source of defence cells, connective tissue. If, on the other hand, the crystals are precipitated within the connective tissue wall of the cyst, then a foreign body reaction occurs.

Fat in the form of droplets also arises in the tissues during cellular degeneration. For instance, in eosinophil granuloma, in which there are localized areas of tissue breakdown, in bone, associated with an infiltration of eosinophils, fat is liberated and numerous phagocytic cells take up the fat droplets. Some of these cells fuse to form giant cells (Walker and Lucas, 1950).

Keratin is a normal constituent of the tissues which can act as a foreign body if it gets into an abnormal situation. In carcinoma of the tongue there may be a very considerable overgrowth of keratin. Though this hyperkeratinization is abnormal, its situation may be normal—on a free epithelial surface. Or again, its situation may be abnormal—in an epithelial pearl. In the latter instance, the keratin is still in contact only with epithelium, but occasionally these pearls break down, when the keratin comes into proximity with connective tissue. A foreign body reaction then occurs.

Case V.—This case illustrates a pathological condition of the gingivæ due to a foreign body reaction in relation to misplaced keratin. The patient, a man of 30, showed marked overgrowth of the gingivæ. In the upper jaw there was no associated gross inflammation while in the lower jaw there was also a marked degree of chronic gingivitis, and pus could be expressed. There was no destruction of bone.

A biopsy showed the appearances seen in Figs. 10, 11 and 12. The surface epithelium is rather thickened and the subepithelial tissues are densely infiltrated with chronic inflammatory cells. In addition, there are islands of isolated epithelium and also areas showing well-marked foreign body reaction (Fig. 10). These reactions appear to be in connexion with masses of very darkly stained material, resembling keratin scales which have undergone calcification (Fig. 11). Fig. 12 shows an island of epithelium which has produced keratin and which has broken open, as it were, so that the keratin is escaping into the connective tissues, where it stimulates a foreign body reaction.

ACKNOWLEDGMENTS

I am indebted to those surgeons who have permitted me to use their clinical records, and to Dr. W. A. Crich and Mr. P. A. Toller for the loan of photographs.

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Mr. Ivor R. Kramer emphasized that foreign body lesions in the oral tissues are not uncommon as he recalled having seen, in the last two years, 15 cases (excluding reactions to cholesterol). Of these 15 cases 2 were proved tuberculous infections, 7 were reactions to silicious materials and 2 were reactions to other foreign bodies. In one of the remainder the gingivæ contained numerous tubercles, some of which appeared to contain fragments of keratinizing epithelium. However, thirteen years earlier the patient had an appendicectomy and the appendix also had been found to contain tubercles. Further investigations showed no evidence of sarcoidosis.

Mr. Kramer mentioned caseation as a feature of value in distinguishing tuberculous infections from other lesions showing tubercle formation. He noted that in one of the photomicrographs shown by Dr. Lucas the giant cells associated with silicious material contained "asteroid" bodies. He had not seen any of these in his own cases, and asked whether Dr. Lucas could give any further information on their incidence in the oral tissues. He also questioned the inclusion of eosinophil granuloma and actinomycosis in the group of conditions giving foreign body reactions, suggesting that in the former the majority of the giant cells might be osteoclasts, and that actinomycosis was a chronic suppurative infection in which the tissue changes were not comparable to those found in the other conditions described.

Professor M. A. Rushton thought the silica particles found in the gums might well be the result of polishing with pastes such as the pumice substitutes used during the war. He was surprised that more foreign body reactions had not been attributed to root filling materials, especially those used in conjunction with apicectomy, since the tissue tolerance to many of these materials at other sites was known to be poor.

Dr. Lucas, in reply, agreed that lesions of the type he had described might not be rare: he had already mentioned that they occurred quite frequently in the tissues in general, though there were relatively few reports in the oral literature. With regard to eosinophil granuloma and actinomycosis, he was not proposing a new basis of classification for these or other diseases. He had merely abstracted certain of their features for purposes of description.

Aneurysm of a Small Vein in the Cheek

By B. E. D. Cooke, L.R.C.P., M.R.C.S., L.D.S.Eng.
(*Dental Pathology Department, London Hospital*)

11.12.50: Miss J. O., aged 17, attended the London Hospital Dental Department complaining of a swelling in the right cheek. One month earlier she had received a blow on the right side of the face with a telephone receiver. This blow was not sufficient to cause a bruise, but it did bring the lump to light and was followed by a slight ache.

On examination there was a tender, cystic, non-pulsatile, mobile swelling 2 cm. diam. in the right cheek. Its lower pole was felt in the buccal sulcus beside $\underline{7}|$, and it was free from attachment to underlying bone or muscle. The buccal mucosa at this site showed a marked dilatation of superficial vessels. $6|$ had slight occlusal caries and $|1$ was a dead tooth with apical infection. Otherwise the teeth and gingivæ were in good condition. On palpation the cervical lymph glands were not enlarged. Radiographs did not reveal any abnormality in the maxillary sinus. The provisional clinical diagnosis lay between a lipoma and a mucus retention cyst.

21.1.51: Operation by Mr. G. T. Hankey for removal of the nodule by an intra-oral approach, under general anæsthesia. A hæmatoma developed which drained through the incision on the first and fifth post-operative days.

Pathology.—Macroscopical examination showed a round soft nodule 1·3 cm. diam., with a smooth, grey brown, outer surface to which was attached a similar smaller nodule 0·4 cm. diam. and tissue shreds. Cut section revealed an outer wall 0·2 cm. thick surrounding a softer core of dark brown tissue flecked with black.

Microscopical examination disclosed a saccular aneurysmal dilatation of a small vein, almost obliterated by an organizing thrombus. Unaltered red cells in the centre of the lumen showed that blood still flowed. The wall of the parent vessel is continuous with that of the aneurysm. It is not easy to be certain that the parent vessel is a vein as opposed to an artery, but the following points favour the former. The internal elastic lamina is ill-defined, and the circular smooth muscle fibres of the media are each separated by fibroblasts and collagen fibres. The adventitia consists of longitudinal bundles of collagen fibres and fibroblasts with an ill-defined elastic lamina. An artery of this size should have well-marked internal and external elastic laminæ, with the muscle fibres of the media set closely together.

The media of the vein continues into the wall of the aneurysm, where in places it has been completely replaced by fibrous tissue, making the aneurysm a false one. The internal elastic lamina is largely absent and the intima has been replaced by granulation tissue. Dilated vessels of the vaso vasorum

FIG. 1.—Section of aneurysm and parent vein. Stained by Mallory's phosphotungstic acid hæmatoxylin. × 7. V, vein. M, smooth muscle in wall of aneurysm. G, granulation tissue.

FIG. 2.—Section showing continuity of vein and the aneurysm. Stained hæmatoxylin and eosin. × 37. V, vein. M, smooth muscle in wall of aneurysm.

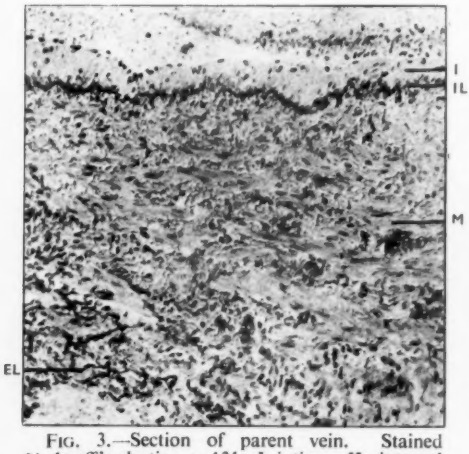

FIG. 3.—Section of parent vein. Stained Verhoeff's elastic. × 131. I, intima. IL, internal elastic lamina. M, smooth muscle fibres, each separated by fibroblasts. EL, external elastic lamina.

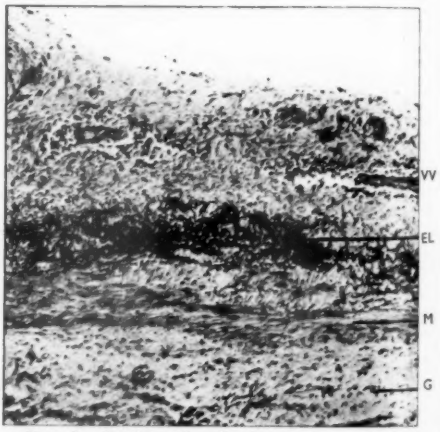

FIG. 4.—Section of wall of aneurysm. Stained Verhoeff's elastic. × 80. VV, vaso vasorum in adventitia. EL, external elastic lamina. M, smooth muscle of media. G, granulation tissue.

of the adventitia are in direct contact through the muscle of the media with capillaries in the granulation tissue.

The parent vein does not appear to show any abnormality either in the intima or the media, so that it is difficult to account for this aneurysm except as a result of trauma. Yet trauma to the cheek is so common and aneurysm so rare. It might well be that the blow only brought to light a congenital abnormality of the vein at this site by causing a thrombus with its subsequent organization.

The "American Illustrated Medical Dictionary", 20th Edition, Dorland, defines an aneurysm as a sac formed by the dilatation of the walls of an artery or of a vein and filled with blood.

Finally may I say how grateful I am to Mr. G. T. Hankey for the clinical history of this case, and to Messrs. J. E. Linder, A. L. Gallup and J. E. Hutchinson for their help in the preparation of the slides and photographs.

Section of Pædiatrics

President—A. G. WATKINS, M.D., F.R.C.P.

[*November* 23, 1951]

Leontiasis Ossea, Skeletal Precocity—possible Albright's Syndrome.—J. G. MILLICHAP, M.D., M.R.C.P. (for CHARLES F. HARRIS, M.D., F.R.C.P.).

B. W., aged 4½ years.

Only child of healthy parents. Not jaundiced at birth. Forehead prominent at birth, remarkably so at 10 months, and gradual enlargement since then (Fig. 1). Recent dacryocystitis. No trauma or bone pain.

Examination.—Intelligent girl, taller and heavier than normal for age. Height 46 in. Span 47 in. Weight 52 lb. Large skull with supra-orbital, mastoid and occipital symmetrical bony swellings. Prominent chin; teeth widely spaced. Blurred margins of left disc. Thyroid not enlarged. No evidence of sexual precocity. Skin not pigmented.

Investigations.—Serum calcium and phosphorus normal. Serum alkaline phosphatase 33 K.A. units. Negative Wassermann reaction. Serum cholesterol 232 mg. per 100 ml. Thymol turbidity 2 units. Urinary 17-ketosteroids 0·5 mg. per day. Mother's Rhesus factor positive.

X-ray report (Dr. G. Simon).—"Skull, abnormal in shape; small sella; large prominence in frontal area consisting of an outer dense cortical layer and an inner trabeculated shadow, suggesting cancellous bone (Fig. 2); similar prominence on the symphysis menti. Advanced bone age. The left radius is

FIG. 1.—Photograph showing frontal swelling.

FIG. 2.—X-ray of skull showing abnormal shape, frontal swelling, and a degree of basilar impression.

abnormally wide in the middle third with a thin cortex and rather structureless cancellous portion.

"*Conclusions.*—Leontiasis ossea, though as a rule the area of increased density (or enlargement) is more structureless. The appearance of the radius is very typical of fibrous dysplasia of bone".

Operation.—Removal of the frontal bony swelling was performed by Professor Sir James Paterson Ross with good cosmetic effect.

Histological report (Dr. R. J. R. Cureton).—Specimen consists of a portion of the outer table of the skull, together with underlying cancellous bone. The trabeculæ are composed of normal lamellar bone separated by a loose vascular adipose tissue, with no appreciable increase in fibrous tissue.

Comment.—The first communication by Albright and his co-workers detailed a triad of abnormalities which included disseminated fibrosis (fibrous dysplasia) of bone, areas of cutaneous pigmentation, and an endocrine disturbance with precocious puberty in females.

The conception of the syndrome has since been widened, and incomplete examples are now recognized (Albright and Reifenstein, 1948).

Skeletal precocity, in evidence here, occurs with greater frequency than sexual precocity, and, unlike the latter, is common to both sexes (Falconer *et al.*, 1942).

The radius exhibits changes regarded by some as typical of fibrous dysplasia. The frontal swelling, however, lacks the characteristic histological features described in previously reported cases of the syndrome.

Unusual microscopical appearances of the bone have been noted by others, (Dockerty *et al.*, 1945). The pathological interpretation itself should therefore not vitiate a diagnosis of Albright's syndrome in this patient.

Sir Thomas Fairbank, who kindly examined the radiographs, considered the bone lesion to be unique and not that of fibrous dysplasia.

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Von Recklinghausen's Disease—Neurofibromatosis with Bone Involvement, Scoliosis and Wedge-shaped Deformity of Thoracic Vertebræ.—A. WHITE FRANKLIN, M.B., B.Ch., F.R.C.P.

S. S., girl aged 5 years, was referred on account of a swelling over the left supra-orbital region and a drooping left eyelid.

On examination she is a healthy, well-covered girl, weighing 39 lb. There is a soft subcutaneous swelling over the left supra-orbital region and a slight droop of the left upper eyelid. A membranous defect can be felt over the left parietal bone. She stands straight but has a lower thoracic scoliosis. There is one café-au-lait patch on the skin of the anterior abdomen. The parents are unrelated; there is one brother aged 9 years and normal. The mother has extensive skin lesions of von Recklinghausen's disease all over the trunk without bone lesions.

X-rays of the spine show two wedge-shaped vertebræ, T.10 and 11 (Fig. 1). X-rays of the skull show defects of ossification in the left parietal and left occipital regions (Fig. 2). No periosteal changes are seen in the X-rays of the skeleton.

FIG. 1.—Wedge-shaped vertebræ (T.10 and 11) in von Recklinghausen's disease.

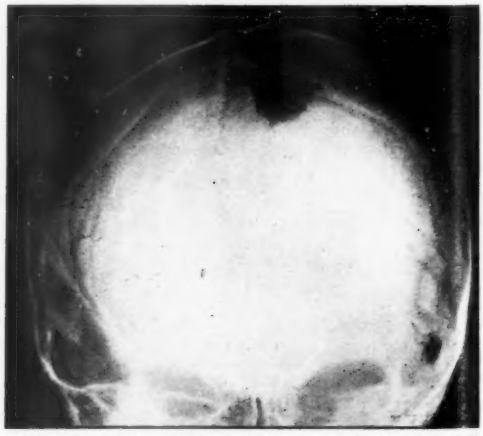

FIG. 2.—Skull showing defective ossification in left parietal and left occipital bones in a case of von Recklinghausen's disease.

Comment.—Scoliosis is reported in this disease, but the vertebræ are said to be normal. There are deformities of two thoracic vertebræ and membranous deficiencies in the skull in this case. The question is whether these are manifestations of neurofibromatosis or whether the patient has two inherited defects. In the latter case presumably there is no risk of deterioration.

Incontinentia Pigmenti (Bloch-Sulzberger).—A. WHITE FRANKLIN, M.B., B.Ch., F.R.C.P.

V. S., girl aged 21 months. She has progressive pigmentation of the skin, first noticed on the left lower limb at the age of 2 months. She is the survivor of premature 32-week twins, the other being stillborn. Birth-weight 3 lb. There were no skin lesions in the neonatal period and her general progress was satisfactory. At 7 months her legs swelled and became hot, and when the swelling subsided more pigmentation was seen; there have been further febrile attacks, sometimes with vomiting, and with further pigmentation. There is, as yet, no sign of fading. Mother and father are normal and unrelated. No family history of skin defect is known.

Examination shows a normal healthy intelligent girl, the only defect being a brown pigmentation on the trunk and on the lower limbs. The lesion shows mainly a linear form but there are complicated patterns, especially on the chest wall. Hair, nails, eyes, and teeth are normal. No abnormal pigments are found in the urine.

13.11.51: Skin biopsy from left chest wall (Dr. R. J. R. Cureton): Sections of the skin show no gross structural changes. The amount of melanin pigment in the basal layers of the epithelium is variable, one section shows a moderate amount, another shows virtually none. All sections show a large number of melanophores containing closely packed melanin granules and situated almost entirely in the superficial corium. The appearances are those described in incontinentia pigmenti.

Comment.—Haber reported the first case in England in April, 1948 (*Proc. R. Soc. Med.*, 1948, 41, 759). 29 case reports have been collated in the literature and the features of these and the present case are summarized. Sex: 26 females, 3 males, 1 not stated.

Condition of the skin at birth: 18 were normal, 5 had erythema with or without blisters, 2 had actual pigmentation, 2 had one pigmented nævus each and the condition of 3 is not stated. Skin lesions were reported in the neonatal period in 11 further cases. Pigmentation was actually present at birth in 2 cases, followed a skin lesion or appeared in normal skin within the first month in 9 cases and before the age of 6 months in 6 cases, and by the age of 3 years in a further 11 cases.

Colour is described as steely grey or blue, slate grey, dark brown, light brown, or café-au-lait, several colours being sometimes seen in one case.

The distribution is mainly on the trunk and upper part of the lower limbs. The lower part of the lower limbs and the upper limbs are less frequently affected. Rarely the scalp, the face, and the mucous membranes are affected.

Fading of the pigmentation, but not complete disappearance, is reported in 12 cases, all but one being over the age of 3 years. In 16 cases there is no fading but 9 of these are under the age of 3 years at the date of the last report.

There is sometimes a family history which may affect more than one generation.

Associated congenital defects are recorded, 6 having a defect of the eye, such as pseudoglioma or opacity of the lens. Ectodermal defects such as patchy alopecia, dental hypoplasia, brittle or spoon-shaped nails have been found and congenital heart disease, microcephaly, and spastic paraplegia have also occurred. Other members of the family may have congenital defects without pigmentation of the skin. The familial character and the association of pigmentation with congenital ectodermal defects support the view that this is a congenital abnormality of the skin.

(A fuller report of this case with photograph and a more detailed account of the literature with references appears in *Brit. med. J.*, 1952, i, 75.)

Relapsing Febrile Nodular Non-suppurative Panniculitis (Weber-Christian Disease.)—A. WHITE FRANKLIN, M.B., B.Ch., F.R.C.P.

D. K., male aged 14 months, attended hospital for painful lumps in the skin. He was born normally at full term, the first and only child of normal, unrelated parents. Birth-weight 7 lb. 12 oz. He was fed on National Dried Milk and grew well, weighing 18 lb. 9 oz. when first seen at 9 months. Apart from the skin condition he has been an entirely normal boy.

The first swelling appeared on the back of the right thigh at 5 months. He was unwell and hot (temperature not recorded). There was swelling and purplish-red discoloration of the skin with moderate tenderness. The colour fades and the lumps disappear in ten to fourteen days. There have been many attacks, the lesions always occurring in the lower limbs. Individual lesions resemble erythema nodosum in size, shape, distribution and colour.

On examination.—Looks normal, and well grown. No enlarged lymph nodes. Spleen not felt. No atrophy where old lesions.

11.10.51: Tuberculin jelly test positive. E.S.R. 28 mm. in the first hour.

W.R. and Kahn negative.

Blood count: Hb 10·4 grammes %; R.B.C. 5,460,000. W.B.C.: Polymorphs. 63% (10,080), leucos. 27% (4,320), monos. 10% (1,600).

Chest X-ray normal.

3.3.51: Section from a lesion in right thigh (Dr. R. J. R. Cureton) shows a widespread inflammatory reaction in adipose tissue. There is a tendency to focal distribution particularly around blood vessels.

The infiltrations consist mainly of polymorphs, large phagocytes, lymphocytes, and occasional eosinophils. No areas of fat necrosis and no foreign-body type of giant cells are seen. The appearances are those described as nodular non-suppurative panniculitis (Weber-Christian disease).

Comment.—The diagnosis in this case depends on the occurrence of repeated febrile illnesses with lesions having the histological features of the Weber-Christian disease. The boy is young for this condition and there have been no evidences, so far, of any atrophy of the subcutaneous tissues on the sites of the lesions. The condition is undoubtedly one of panniculitis and this had led to a consideration of other forms of subcutaneous fat change found in pædiatrics. The nomenclature of these conditions has been somewhat confused, especially the use of the word sclerema, or pseudo-sclerema, and the suggestion is here made that the whole group should be included under the general heading of panniculitis of the various types indicated in the Table. This is based on the suggestion made by Dr. Alice Carleton in "Further Rare Diseases" (ed. F. Parkes Weber, 1949, Lond. & New York). She describes a case of Weber-Christian disease in which the distribution of the lesions follows very closely on what is usually seen in sclerema neonatorum. Apart from the obvious difference in age, the presence of scarring where the lesions have healed is not seen in the classical case of sclerema neonatorum. However, Dr. Holzel (1951) has recently described a case in the newborn baby where scarring was found. It is generally accepted that the crystals seen in sections of the skin in sclerema are crystals of fat which has altered its physical state, possibly because of a difference in chemical composition. Harrison (1926) showed that the proportion of oleic acid in the subcutaneous fat in cases of sclerema was 65% compared with the normal value for older people of 85%. This difference is considered to be capable of raising the melting point of fat. There is no information available about the chemical composition of subcutaneous fat in cases of Weber-Christian disease.

Table I includes the suggestions for pædiatric additions to Dr. Carleton's classification, the new entries being in italics.

TABLE I.—PANNICULITIS

Based on Carleton (1949), alterations in italics

1. SECONDARY – a direct response to neighbouring tissue disturbance, e.g. phlebitis, tumour metastases
2. TRAUMATIC
   - *a*– due to mechanical injury, blows, pressure, *forceps pressure in the newborn*
   - *b*– chemical injury, e.g. subcutaneous injections of camphor in oil, ? *saline solutions*
   - *c*– thermal injury by heat or cold
   - *d*– bacterial toxins
3. *AGONAL* – *terminally with severe birth trauma or gastro-enteritis in first six months*
4. PRIMARY PANNICULITIS
   - *a*– Weber-Christian disease
   - *b*– Rothmann-Makai disease
   - *c*– *Sclerema neonatorum* (or ? primary panniculitis of the newborn) also known as pseudo-sclerema and subcutaneous fat necrosis.

In addition to panniculitis, it is certain that some cases of severely ill babies who develop the clinical picture of sclerema and sclerœdema neonatorum are suffering from œdema of the skin alone without any change in the histological appearance or physical state of the subcutaneous fat.

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Sclerœdema and Myositis (?Panniculitis).—B. MCNICHOLL, M.D., M.R.C.P.,) for A. DOYNE BELL, D.M., F.R.C.P.).

K. M., male aged 2 years 3 months. Ninth child of healthy parents, others well.

Ten days before admission on 25.7.51, swelling in right side of neck which his mother thought to be a gland and which increased rapidly in size; slight sore throat.

On admission, oval inflammatory swelling 5 × 4 cm. around middle third of sternomastoid and attached to skin but not fluctuant. Moderate pyrexia, but normal E.S.R. and no leucocytosis. Tuberculin negative up to 1/100 O.T. and 0·005 mg. P.P.D. Histoplasmin 1/100 negative; Wassermann and Kahn reactions negative.

Six days after admission small swelling deep in soft tissues in left maxillary region, skin unaffected; this gradually increased in size and soon both lesions showed considerable inflammatory signs, the skin having a dusky red hue and the child becoming more febrile and fretful.

Biopsy of mass in neck 14.8.51.—Gritty white tissue found invading the sternomastoid. Histology showed a necrotizing inflammatory reaction in the fatty tissues with giant cells, histiocytes, lymphocytes and many plasma cells, invading muscle; no tubercles were seen. (Report by Dr. W. E. D. Evans.)

Cannula biopsy of mass in cheek 24.8.51.—Very gritty tissue again; similar histology. Aerobic and anaerobic cultures negative.

1.9.51: Inflammatory reaction reached its peak, with moderate constitutional disturbance; the mass in the cheek was almost stony hard, the skin a dusky red, tense and adherent, with some desquamation at the lower limits (Fig. 1); the eye was almost closed by œdema. At this time the leucocyte count was 4,700, with equal numbers of granulocytes and lymphocytes.

FIG. 1.—Swelling in cheek at its peak, five weeks after the onset, with desquamation at the lower periphery.

15.9.51: Gradual improvement commenced, both lesions appeared as solid purplish plaques with well-defined edges; the raised edge of the neck lesions now crept slowly outwards on to the face and round the neck beyond the mid-line in front and behind, leaving the skin in the centre relatively normal. The lesion in the cheek assumed a similar annular form, the raised edge also having a violaceous hue and extending to the pinna.

16.10.51: Urinary creatine 280 mg. *per diem.* Urinary creatinine 150 mg. *per diem.*

Normal values in male aged 2½: Creatine 80 mg. *per diem.* Creatinine 190 mg. *per diem.* (Bodansky and Bodansky).

20.11.51: General condition good; fresh plaque appearing above nasion, other lesions slowly resolving.

Treatment.—At first penicillin and chloromycetin were used in large doses without effect. Possible improvement followed the use of streptomycin combined with para-aminosalicylic acid (PAS); later gradual improvement coincided with the use of Lugol's iodine 15 minims daily.

Comment.—This condition does not seem to correspond to any well-known entity, hence the non-specific title. The involvement of muscle and the moderate creatinuria could be part of a dermatomyositis, but the localized nature and absence of any demonstrable muscular weakness are against this diagnosis. The very marked hard inflammatory swelling in the cheek, followed by the peculiar creeping annular lesion is most unusual. The term *panniculitis*, as used by Parkes Weber and Gray in 1924 in describing their cases of "chronic relapsing polydermatomyositis with predominant involvement of the subcutaneous fat", seems to come nearest to the pathological condition in this child. Similar cases have since been given the name of Weber-Christian disease, but none corresponds closely to the present case. It seems reasonable to hope that the prognosis may be good.

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Ectodermal Dysplasia with Congenital Absence of the Breasts.—E. M. POULTON, M.R.C.P., D.C.H., D.P.H., (for E. HINDEN, M.D., M.R.C.P.).

T. G., girl aged 3½ years.

Family history.—No other known sufferers from ectodermal dysplasia in the family. During a later pregnancy the mother was found to have a strongly positive Wassermann reaction.

History of development.—Milestones of childhood passed normally. Finger-nails noticed to grow very slowly, and seldom needed cutting. Toe-nails have never been cut since birth. Hair always sparse and fine. Teeth scanty and erupted irregularly. No trace of breasts or nipples.

Investigations.—W.R. and Kahn negative. Serum cholesterol 127 mg. per 100 ml.
Blood count: Hb 66%. R.B.C. 3,100,000; C.I. 1·0; W.B.C. 7,200. Differential normal.
X-ray of mandible: Only two lower deciduous teeth present. Many tooth-buds of the permanent dentition missing.

Comment.—There have been some 30 cases of amastia published, only 2 in the past ten years. In most of these the defect was unilateral, and associated with deformity, either of the underlying chest wall, or of the upper extremity on the same side. We are not aware of another case in which complete bilateral amastia, without such deformity, has occurred as part of an ectodermal dysplasia.

Acute Nephritis (Microscope Sections Shown).—J. J. KEMPTON, M.D., M.R.C.P.

P. W., male aged 2 years.

The child had been well until the evening before admission, when a transient shivering attack was noticed. The following morning he seemed perfectly well and ate his normal breakfast. Fits commenced suddenly during the afternoon, and on arrival at hospital two hours later there were continuous generalized convulsions. He was semiconscious; limbs were stiff and there was a very marked trismus. No abnormal physical signs could be found in heart, chest or abdomen; blood pressure was 120/90; pupils were normal; fundi not well seen, appeared normal. It was not possible to see the throat until some pentothal had been given; the fauces were slightly injected. Urine was passed into the bed, and no further specimen was obtained. A scratch mark was noticed on one arm. A provisional diagnosis of tetanus was made and 100,000 units of antitoxin were given intravenously. The child's condition deteriorated rapidly, breathing becoming at first automatic and then intermittent, and he died about six hours after the onset of symptoms. At post-mortem all organs, including brain and kidneys, were normal to naked-eye examination. Section of kidneys showed an acute glomerulo-nephritis (Fig. 1).

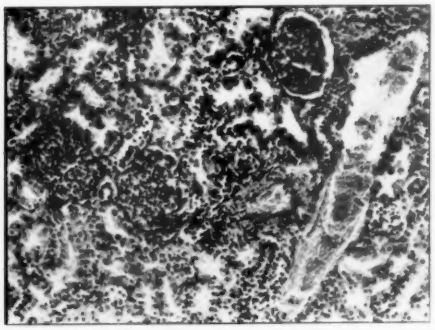

FIG. 1.—Kidney showing acute glomerular changes. Tubules and vessels, including the afferent arteriole where this is seen, are normal. × 105.

Comment.—Acute nephritis is a rare cause of sudden death, though cases have recently been reported in which, death having been thought to be due to asphyxia, similar acute glomerular changes had been found at autopsy. The importance of detailed histological investigation in cases of sudden death is underlined by this case.

Hand-Schüller-Christian Syndrome. Treated with Deep X-rays.—CLIVE UPJOHN, M.D., M.R.C.P. D.C.H.

M. B., aged 3 years. Referred originally, aged 2 years, on account of failure to thrive, associated with pale offensive stools, distended abdomen, and anæmia. Stature significantly small and under weight for his age. Clinical examination, and all other investigations negative. Blood transfusion given for anæmia. Stools—fæcal fats 26%. Hb 50%.

After an interval of four months, had developed bilateral exophthalmos and splenomegaly. X-ray of skeleton showed typical appearance of Hand-Schüller-Christian syndrome in skull (Fig. 1A) and in left iliac bone of pelvis. Subsequently also developed thirst and polyuria.

A course of radiotherapy to affected bony areas given under the supervision of Mr. Jackson Richmond at St. Luke's Hospital, Guildford. General condition much improved, and local radiological appearances showed resolution (Fig. 1B).

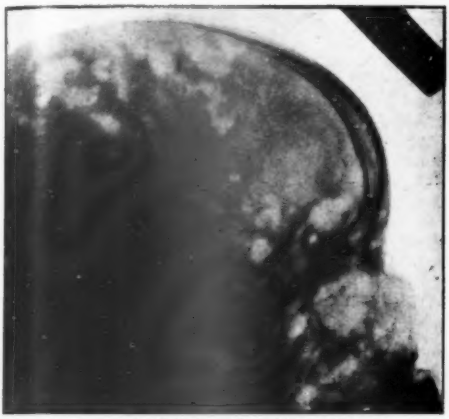

FIG. 1A.—Skull before deep X-ray therapy.

FIG. 1B.—Skull after deep X-ray therapy.

DISCUSSION

Advice was requested regarding the prognosis and possible benefit from further course of radiotherapy. No comment was made regarding this aspect but one speaker suggested that cortisone might be beneficial in view of his experience following the use of this drug in the allied condition of Letterer-Siwe syndrome.

Focal Intracranial Calcification with Convulsions and Hemiparesis.—M. E. PENDLETON, M.D. (for REGINALD LIGHTWOOD, M.D., F.R.C.P.).

A. M., male, aged 3 years 11 months.

First admission to St. Mary's Hospital, aged 18 months, because of left-sided convulsions and hemiplegia first noted at 15½ months.

Past history.—Normal birth, growth, and development. Gastro-enteritis at 13 months. Fall on head at 15 months, two weeks before first convulsion, without immediate sequelæ.

Family history.—Not relevant.

Physical examination.—Mild left hemiparesis only. Optic fundi normal.

Investigations.—Skull X-rays negative. C.S.F. normal. EEG slight amplitude asymmetry, left greater than right; suggestive of idiopathic epilepsy.

Progress.—Convulsions persisted up to four per day, despite phenobarbitone and phenytoin. Left hemiplegia improved with physiotherapy. Speech was slurred. No further physical changes, mental development apparently normal.

Second admission to St. Mary's Hospital, aged 3 years 10 months, because X-rays of skull showed localized right parietal calcification. On examination, findings essentially unchanged.

Investigations.—Wassermann reaction, Mantoux 1 : 10, and toxoplasma complement-fixation tests negative. Serum calcium and phosphorus normal.

The patient was transferred to the National Hospital, Queen Square. A pneumo-encephalogram disclosed a near-normal ventricular system, with an abnormal pooling of air immediately to the right of the mid-line in the parietal region, just above the corpus callosum, near the area of calcification. Cerebral arteriogram showed no shift of the vascular system, but a bowing of the anterior cerebral artery away from the area of calcification. Mr. Wylie McKissock believed the child had a parasagittal tumour, possibly a meningioma. At operation, he exposed a large right parietal tumour,

which could be only partially excised, although enough was removed to provide good internal decompression.

Pathological report.—Ganglioglioma.

Progress.—Transferred to St. Luke's Hospital, Guildford, for deep X-ray therapy. Condition much as before operation.

Congenital Pseudo-arthrosis in a Newborn Infant.—DAVID MORRIS, M.R.C.P., D.C.H., (for RICHARD H. DOBBS, M.D., F.R.C.P., and J. C. R. HINDENACH, F.R.C.S.).

C. H., male. Birth-weight 6 lb. 12 oz.

Born of apparently healthy parents after an uneventful pregnancy and a normal delivery. He was the youngest of a family of 9; all were alive and well. Soon after birth, the shape of the left leg was noted to be abnormal and was suggestive of a fracture. An X-ray revealed a fracture of the left tibia with an abnormal appearance of the bones at the fracture site (Fig. 1). A diagnosis of congenital pseudo-arthrosis was made. No other abnormal clinical signs were found.

To promote bony union, the fibula was forcibly fractured and an attempt made to approximate the fracture ends of the tibia. In spite of repeated immobilizations in plaster of Paris for one year, there was no evidence of healing of the fracture (Fig. 2). During the year, café-au-lait patches appeared

FIG. 1.—X-ray taken 9.10.50.

FIG. 2.—X-ray taken 4.10.51.

over the trunk, back and abdomen; in the posterior cervical triangle small discrete painless nodules could be felt. Neurofibromatosis was suspected and on examination of the whole family, similar lesions were found in the father, a brother, and to a marked degree in a sister. Her skeleton was X-rayed but no bony abnormality was detected. In view of the cutaneous lesions and the nodules, the child was presented as suffering from congenital pseudo-arthrosis associated with neurofibromatosis. In the discussion, the non-union of the fibula was emphasized and mention was made of the fact that osseous lesions due to neurofibromatosis usually caused some lengthening of the limb and that in this case there was shortening.

The following cases were also shown:

Double Aortic Arch (Operation Result).—Mr. E. G. DOLTON and Dr. H. EVERLEY JONES. (An account of this case is included in "Congenital Anomalies of the Aortic Arch," *Lancet*, 1952, i, 537.)

Pulmonary Hæmosiderosis.—Dr. J. N. O'REILLY. (This case will be published in the *British Journal of Radiology*.)

Section of Neurology

President—Professor P. C. P. CLOAKE, M.D., F.R.C.P.

[*November* 1, 1951]

MEETING AT THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON, W.C.1

Carotico-cavernous Fistula Causing Pulsating Exophthalmos with Cerebral Blood-flow Maintained Through External Carotid Artery.—M. A. FALCONER, M.Ch., and R. D. HOARE, D.M.R.D.

E. C., male, aged 41.

History.—In 1944 patient was knocked unconscious in a road accident. Post-traumatic amnesia of between ten and fourteen days' duration. On regaining his senses, patient found that he was blind in the left eye, had a rushing noise in his head, and a protuberant left eyeball. Since then the degree of ocular protrusion has remained stationary, but a subcutaneous venous channel to the left side of his nose has steadily increased in prominence. Between 1948 and June 1951 he experienced about a dozen nose-bleeds, some necessitating admission to hospital. All were from the left nostril. In July and August 1951 he had a further dozen nose-bleeds, some of moderate severity.

Examination.—An otherwise healthy man. Presented well-marked pulsating exophthalmos on left side (Fig. 1). Arterial pulsations together with a thrill palpable over distended subcutaneous orbital

FIG. 1.—Appearance on admission.

veins. Left eye blind with primary optic atrophy. Slight impairment of function of V, VI, and VII cranial nerves on left side, evidently sequelæ of head injury. Loud bruit audible over anterior part of head, most intensely over left orbit; this disappeared when the left carotid artery was compressed in the neck. B.P. 110/65.

Investigations.—The only abnormal feature in X-rays of the skull was a marked widening of the left sphenoidal fissure. The optic foramina were of normal size.

Various tests of the collateral blood-supply to the left cerebral hemisphere seemed, at first, to indicate that carotid ligation, which is usually regarded as the standard treatment of pulsating exophthalmos, would not be tolerated.

(1) Digital compression of the left common carotid artery (Matas' test) continued for 8 to 10 seconds produced loss of consciousness with a right-sided hemiplegia. When a simultaneous EEG record was taken, medium-voltage slow-wave activity at 3–4 c/s appeared over the left hemisphere (Dr. J. V. Gordon).

(2) A similar loss of consciousness, but with a left-sided hemiplegia, appeared within a few seconds when the right common carotid artery was compressed.

(3) Percutaneous left carotid arteriography demonstrated that the left internal carotid artery was emptying into the cavernous sinus and thence into dilated veins in the orbit, sylvian region, and middle cranial fossa; in addition the left anterior and middle cerebral arteries were faintly filled (Fig. 2). The arteriograms were repeated several times, and in most films the density of contrast

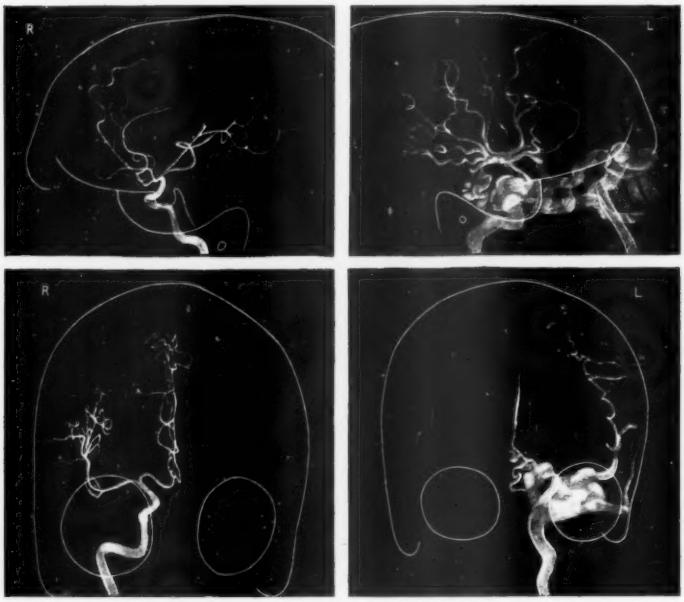

FIG. 2.—Tracings of pre-operative arteriograms.

medium within the cerebral arteries was much less than that within the veins. In one chance exposure, however, the bulk of the contrast medium had entered the external carotid artery, and in this particular film the anterior and middle cerebral arteries were well shown.

(4) Percutaneous right carotid arteriography outlined only the branches of its own arterial tree (Fig. 2). No trace of contrast medium appeared in the left cerebral arteries. In our experience this is contrary to what usually happens with a large carotico-cavernous fistula, for generally so much blood is shunted from the affected internal carotid artery into the cavernous sinus, that the contralateral carotid artery is called upon to supply both cerebral hemispheres.

We therefore deduced that there must be a defect of the anterior communicating artery, and that this defect also accounted for the loss of consciousness and hemiplegia provoked by the Matas' compression test. It thus seemed *prima facie* that we would be unable to treat this patient by the time-honoured remedy of common carotid ligation (Travers, 1811). However, attacks of nose-bleeding had become alarmingly frequent and severe. We therefore decided to pursue the clue afforded us fortuitously by the observation relating to the left external carotid artery.

Operation.—Under local analgesia and with aseptic surgical technique, the left internal and external carotid arteries were exposed in the neck at their origin from the common carotid artery, and in turn were then injected under direct vision with 35% diodone B.P. The left internal carotid arteriogram so obtained disclosed that practically all the blood flowing through the artery was being diverted into the cavernous sinus and thence to the veins of the orbit and middle cranial fossa; none of the contrast

medium appeared in the cerebral arteries (Fig. 3). The left external carotid arteriogram, however, showed that several branches of the internal maxillary artery were anastomosing with branches of the ophthalmic artery, and that through these connexions the external carotid artery was supplying blood retrogradely to the ophthalmic artery, and thence to the intracranial portion of the internal

FIG. 3.—Left internal carotid arteriogram (retouched).

FIG. 4.—Left external carotid arteriogram (retouched).

carotid artery and to the left anterior and middle cerebral arteries. Some of the contrast medium passed downwards in the internal carotid artery from the ophthalmic artery towards the fistula (Fig. 4).

We next determined to test the effect of occlusion of the left internal carotid artery. At a preliminary stage the common carotid artery had been occluded with a Crile's arterial clamp, but as the patient became unconscious within a few seconds the clamp had to be released. When the internal carotid artery was clamped, however, the patient became restless for a few seconds; but continued to talk and to move his limbs, while the ocular protrusion lessened and the bruit became softer. The clamping was continued for twenty minutes, and then, as no untoward symptoms had appeared, the internal carotid artery was tied tightly with a silk ligature.

FIG. 5.—Photographs showing degree of ocular protrusion before carotid ligation (left) and afterwards (right).

Results.—Convalescence was smooth, and there was no sign of hemiparesis. The recession of the left eyeball has only been slight (Fig. 5), but there has been a marked lessening of tension in the orbital veins, while the bruit has subsided to a third of its former intensity. The thrill palpable over

the orbit has disappeared. No further nose-bleeds have occurred. Percutaneous left carotid arteriography shows that the collateral circulation through the external carotid and ophthalmic arteries is now feeding the carotico-cavernous fistula as well as supplying the left cerebral arteries; there is no filling of the internal carotid artery in the neck.

It is interesting that unilateral digital compression of either common carotid artery still produces within 8 to 12 seconds a loss of consciousness associated with a contralateral hemiplegia and the appearance of delta activity in the EEG (Dr. J. V. Gordon). Since operation we have maintained the unilateral compression for longer periods, and have found that within a further 20 seconds, compression still being maintained, these effects disappear. Then apart from an occasional slow wave (and associated myoclonic jerk) the EEG record remains normal until, after a total period of one and a half minutes' compression of the left common carotid artery (or two and a half minutes for the right common carotid artery), continuous slow-wave activity reappears associated with contralateral hemiparesis, and consciousness is again lost. These effects then continue for as long as compression is maintained, but because of their disturbing character we have not maintained the compression for longer than three minutes.

Comments.—The chief interest in this case is the demonstration of the collateral circulation to the anterior and middle cerebral arteries via the external carotid and ophthalmic arteries. This collateral circulation appears to be maintaining the blood supply to the anterior part of the cerebral hemisphere. Such a circulation has been mentioned previously but not illustrated by Bull (1951), by Denny-Brown (1951), and by Torkildsen and Koppang (1951), as occurring sometimes in cases of internal carotid thrombosis. It would seem to be of slow development, occurring in cases where there has been gradual occlusion of the internal carotid artery. It is doubtful if this collateral circulation can take over the blood supply to the brain in the event of sudden occlusion of the internal carotid artery.

This, as far as we are aware, is the first time this circulation has been demonstrated in a case of carotico-cavernous fistula. The factor which led to its production is presumably the defect in the anterior communicating artery. In three previous cases of carotico-cavernous fistula we found on percutaneous arteriography that little, if any, of the blood which passed up the carotid arterial system on the same side of the fistula reached the cerebral vessels; instead it was shunted into the cavernous sinus. On the other hand the contralateral carotid supplied not only the cerebral vessels on its own side, but also through the circle of Willis the anterior and middle cerebral arteries on the same side as the fistula. Thus in each case it was possible to "trap" the fistula by Dandy's method (1937), performing firstly an intracranial clipping of the internal carotid artery just below the level of the posterior communicating artery, followed at the same operative session by a ligation of the internal carotid artery in the neck.

Such an approach would have been disastrous in our patient, for the intracranial clipping would perforce have been above the level of the ophthalmic artery, and so would have cut off the blood supply to a large part of the left cerebral hemisphere. Even ligation of the common carotid artery, which Meadows (1951) describes as the standard treatment for carotico-cavernous fistula, was not practicable for it would have interfered with the cerebral circulation. We have benefited our patient by internal carotid ligation, but not cured him. Theoretically to cure him we would now have to occlude the internal carotid artery above the fistula and yet below the origin of the ophthalmic artery. This is not possible for anatomical reasons.

The question also arises as to whether the development of such a collateral circulation to the brain via the external carotid and ophthalmic arteries accounts for some of the cases, in which the symptoms of carotico-cavernous fistula or other vascular lesions have returned after a period of transitory disappearance following internal carotid ligation.

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Tuberous Sclerosis with ? Melorheostosis.—J. HAMILTON PATERSON, M.D.

P. G., female, aged 6¾. Admitted to the Atkinson Morley Hospital under Mr. Wylie McKissock, complaining of headaches and vomiting of increasing severity for six months.

Past history.—Normal birth at full term. First noticed to have a squint and deformed fingers of the left hand at about 1 year of age. When 14 months old she had at least two generalized convulsions.

Family history.—No history of epilepsy or any other neurological disorder obtained.

Examination.—Alert and co-operative. Fundi: right obscured by a vitreous opacity, left showed moderate papilloedema. Marked right external rectus paresis.

Skin: Two small nævi seen on right forehead, no facial adenomata.

Digits: Left middle and index fingers enlarged and deformed.

Investigations.—EEG: Very abnormal records obtained suggesting symptomatic epilepsy with multiple foci. X-rays of left hand showed thickening and deformation of the index and middle fingers by an irregular subperiosteal deposition of rather sclerotic new bone. X-rays of chest normal. X-rays of skull revealed four to five small calcified foci situated in the neighbourhood of the right lateral ventricle. Ventriculography showed an oval mass lying between the lateral ventricles and producing a filling defect in the lower and medial aspects of the dilated anterior horn of the right ventricle. The calcified foci described above were seen to lie in and posterior to this mass.

At operation (Mr. Wylie McKissock) a soft reddish-purple tumour was seen arising from the floor of the right lateral ventricle. Portions removed for histological examination showed the appearances of an atypical glioma.

Comment.—The principal diagnosis proffered is that of tuberous sclerosis complicated by a glioma of the floor of the right lateral ventricle. Furthermore, it is suggested that the clinical and radiological features of the deformity of the left hand closely resemble those described by G. S. Hall (1943, *Quart. J. med.*, **12**, 77) in a boy with tuberous sclerosis. He concluded that they were due to melorheostosis.

Dr. G. S. Hall agreed with the views expressed by Dr. Hamilton Paterson and added that as far as he was aware no other examples of the association of tuberous sclerosis with melorheostosis had as yet been described.

Exophthalmic Ophthalmoplegia with Gross Papilloedema.—W. J. BURKE, M.R.C.P. (for S. P. MEADOWS, M.D., F.R.C.P.)

S. F., male, aged 42. Lighterman. Admitted to National Hospital, Queen Square, on 8.8.51.

He had been well until September 1949 when he noticed increasing dyspnœa on exertion, loss of weight, sweats, nervousness and increased "looseness of the bowels". The B.M.R. reading at this stage was + 29%. From September 1949 he had six months' medical treatment (thiouracil). He made a general improvement but relapsed, with a return of his old symptoms in January 1951.

2.3.51: Subtotal thyroidectomy, following fifteen days' preparation by rest and iodine therapy. Prominence of both eyes appeared quite suddenly on 19.3.51 (seventeen days after operation). Within two days he was unable to close his eyes and his vision at the same time rapidly deteriorated.

Bilateral tarsorrhaphies were performed on 30.4.51.

His vision had not noticeably altered in the past four months.

He had noticed intermittent diplopia during the past month, especially on looking upwards.

Since June 1951 he had complained of momentary "blackouts" of vision on suddenly standing, or moving the head.

On examination.—Marked bilateral proptosis, about equal left and right. Moderate periorbital œdema and suffusion of the conjunctivæ.

Pupils equal and react briskly to light and accommodation. Marked restriction of all external ocular movements: upward movement almost completely abolished; lateral movements about 30% of normal; downward movements, gross restriction. V.A.R. 1/60. V.A.L. 1/60. (Correctable to 6/18 on both sides.) There was bilateral massive papilloedema (5–6 D) of rather chronic type. Peripheral fields full. Small bilateral relative centrocæcal scotomata.

Fine irregular tremor of outstretched upper limbs. No other abnormalities noted. Deep reflexes present and equal. Plantars flexor. B.P. 160/105. Pulse 70 per minute. Regular. Thyroidectomy scar well healed. No underlying tumour palpable.

14.8.51: Decompression of left orbit (Mr. Harvey Jackson). Bone was removed from lateral wall of orbit and posterior portion of roof. Orbital fascia tense. Contents of orbit firm and swollen.

24.8.51: Right orbital decompression. Similar findings and procedure.

Histological examination (Dr. W. G. Mair).—*Left temporalis*: "No cellular infiltration or fibrous replacement is seen. It appears healthy."

Left external rectus: "Extensive replacement of muscle fibres by connective tissue. Some muscle fibres are large and possess a greatly enlarged hyperchromatic nucleus and the cytoplasm of these cells stains less deeply than usual. Small round-cell, plasma-cell and occasional polymorphonuclear infiltration occurs around the nerve fibres and blood vessels."

Progress (until 30.10.51).—Definite diminution in degree of proptosis. Still has moderate bilateral periorbital œdema. No objective improvement in visual acuity. Papilloedema remains massive. Upward movement: 30°; lateral movements: 20–30°; downward movements: very little.

Peripheral Neuritis and Carcinoma of Bronchus.—K. W. G. HEATHFIELD, M.D., M.R.C.P. (for J. W. ALDREN TURNER, F.R.C.P.).

B. W., aged 65, a carpenter. For more than thirty years chronic bronchitis, worse in winter. Two years and one year ago attacks of bronchitis lasting two weeks—in the second sputum flecked with blood. Since then progressive exertional dyspnœa, loss of appetite, and loss of more than 1 st. in weight. Dietary intake poor for some months, and recently some dysphagia with sensation of food sticking behind the sternum. Three months ago became unsteady on walking, especially when turning

round. At same time legs became weak both at the hips and knees, as in rising from a chair and going downstairs, and also dorsiflexion of ankles, tending to catch his toes. Slight weakness of grip. No sensory symptoms.

On examination.—Sallow and wasted. Tongue red and glazed. Koilonychia. Chest emphysematous, scattered added sounds. Heart and abdomen normal. Blood pressure 155/95. Cranial nerves normal. Arms: generalized wasting, poor grip, otherwise normal. Legs: marked wasting of calves, weakness of hip flexors and extensors, and extensors of feet. Gait: wide-based and ataxic. Sensation: normal apart from some impairment of pin-prick over the shins, and distal impairment of vibration in legs; position sense normal. Marked tenderness of calves. Arm reflexes normal, knee-jerks just obtainable, ankle-jerks absent, plantars flexor.

Investigations.—X-ray chest—large hilar mass with collapse of right upper lobe. Barium swallow—narrowing of œsophagus with delay at level of hilar shadow. Bronchoscopy—right main bronchus narrowed, and right upper lobe orifice grossly narrowed by external compression; no suitable tissue for biopsy. Œsophagoscopy—slight narrowing of junction of upper third and lower two-thirds.

Blood count: Hb 74%; R.B.C. 5,100,000; C.I. 0·7. W.R. negative. E.S.R. 37 mm. in the first hour (Westergren). C.S.F.—Protein, 45 mg.; cells, 3 lymphocytes. Fractional test meal: complete histamine-fast achlorhydria.

Blood pyruvate tolerance test (Professor R. H. S. Thompson):

	16.10.51	7.11.51	Mean normal
Fasting	1·23	0·93	0·76 mg.%
60 minutes after 50 grammes glucose ..	1·42	1·29	0·92
90 " " " " " ..	1·71	1·45	0·94

After two weeks' treatment with intravenous thiamine, 100 mg. daily, riboflavin, 50 mg. and nicotinic acid 50 mg. q.d.s., there was considerable improvement in the neuropathy, sensation returned to normal and calf tenderness disappeared, ankle-jerks present on reinforcement, and motor power a little improved; ataxy and hip weakness persisted.

Comment.—Peripheral neuritis associated with bronchial carcinoma may be of several types. Here the condition—predominantly motor—appeared to be of nutritional origin conditioned by the achylia; there was an associated nicotinic deficiency glossitis. The peripheral neuritis improved with administration of vitamin B_1 parentally, and the pyruvate tolerance returned practically to normal.

Sensory Neuropathy.—M. KREMER, M.D., F.R.C.P., and R. T. C. PRATT, D.M., M.R.C.P., D.P.M.

Mrs. D. H., aged 59.

3.10.49 to 24.11.49: In Guy's Hospital (Sir Charles Symonds) with a history of eight months' numbness, initially of the left elbow, later affecting at irregular intervals the anterior aspect of both thighs, both arms, the back of the right thigh and the left side of the face.

C.S.F. protein 200 mg.%, later 90 mg.%. Diagnosis: posterior radiculitis.

Following discharge the numbness grew worse and by February 1950 she was unable to walk or to feed herself.

25.3.50: Readmitted to Guy's Hospital. The numbness then involved the whole body, including the tongue.

On examination.—Hypalgesia right fifth nerve. Diminution of power in the arms, absence of reflexes, and loss of sense of passive movement in the hands and feet.

21.3.51: On discharge she showed, in addition, irregularity of the pupils with inequality R<L and impairment of the reaction to light.

16.8.51: Admitted to Middlesex Hospital (Dr. Michael Kremer). She had deteriorated over the previous five months, with increase of numbness and ataxia, difficulty in swallowing, double vision on deviation of the eyes, progressive deafness on the right side, and attacks of retention of urine.

Cranial nerves.—Pupils: R. small, poor reaction to light, good to convergence; L. large, no reaction to light or convergence. Nystagmus on lateral and vertical gaze; right nerve deafness with absent caloric reactions. Loss of sense of passive movement of the tongue and ears.

Arms: Loss of power 50%. Tendon reflexes absent. Loss of sense of passive movement including the shoulder-joints.

Legs: Power full. Tendon reflexes absent. Plantars extensor. Loss of sense of passive movement including the hips.

There was a generalized loss to light and heavy touch, a delayed appreciation of temperature and a raising of the pain threshold with over-reaction. C.S.F. protein 80 mg.%.

Large hard fixed mass in the posterior triangle. Histological report (Dr. A. C. Thackray): poorly differentiated carcinoma.

Results of pyruvate tolerance tests after 50 grammes glucose at 0 and 30 minutes.—

	Date	Minutes 0	60	90
	30.3.50	2·08	2·73	2·23 mg.%
	5.4.50	2·48	2·20	2·18
After 100 mg. thiamine I.M. for 18 days.. ..	24.4.50	2·07	2·14	2·40
After two M.R.C. courses of BAL	5.5.50	1·73	1·92	2·12
	6.9.51	1·34	1·20	1·20
	24.9.51	0·85		

Organic Dementia of Obscure Origin.—PETER K. ROBINSON, M.B., M.R.C.P. (for DENIS WILLIAMS, M.D., F.R.C.P.).

A 34-year-old Cornish farmer with normal previous medical and family history. No epilepsy.

January 1951: Had an illness with anorexia and weight loss, called "influenza".

May 1951: First epileptic fit followed by a period of confusion necessitating admission to Bodmin Mental Hospital for eleven weeks. No abnormal signs. Recovery and return home.

August 1951: Admitted to Royal Cornwall Infirmary with slight dementia. C.S.F. revealed 95 cells/c.mm. (90% lymphocytes) and 1,000 mg.% protein. Seen by Dr. N. S. Alcock who considered the patient should be transferred to the Atkinson Morley Hospital. Here ventriculogram suggested very slight symmetrical ventricular dilatation. EEG showed no major local focus of abnormality.

October 1951: Admitted to the National Hospital. He had slight neck rigidity and was almost moribund, following two convulsions in the post-ventriculogram period. Slow recovery, with residual slight confusion and minimal left hemiplegia. C.S.F. shows 32 cells/c.mm., 320 mg.% protein, 600 mg.% chlorides, 43 mg.% sugar. No porphyrinuria. Mantoux test negative to 1/100 Old Tuberculin.

LUMBAR C.S.F.

Date	Cells (white)	Protein (mg.%)	Sugar (mg.%)	Chlorides (mg.%)
August 1951	95 90% L. 10% P.	1,000	Reduced	610
September 1951	160	—	Normal	—
	100	200	Normal	640
1.10.51	48 45 L. 3 P.	200	40	620
4.10.51	11 9 L. 2 P.	320	42	640
12.10.51	8 6 L. 2 P.	640	—	—
22.10.51	32 19 L. 13 P.	320	43	600

Repeated examinations and cultures for tubercle bacilli and yeasts have proved negative.

Investigations.—Blood count, 26.9.51: R.B.C. 4,490,000. Hb 13·3 grammes. W.B.C. 13,200 (polys. 88%, lymphos. 6%, monos. 5%, eosinos. 1%). B.S.R. 14 mm. in first hour. Blood count, 1.11.51: W.B.C. 10,600 (polys. 84%, lymphos. 12%, monos. 3%, eosinos. 1%). E.S.R. 37 mm. in first hour, 50 mm. in second hour (Westergren.)

Blood urea 45 mg.%.

Wassermann reaction (blood and C.S.F.) negative.

Liver function tests normal (except for raised alkaline phosphatase). No porphyrins.

Mantoux negative at 1/100 Old Tuberculin.

EEG, September 1951: Showed unstable alpha rhythm of 9–11/sec. which was disturbed over the anterior part of both hemispheres by runs of 4–6/sec. waves. No epileptic discharges recorded. October 1951: Low voltage alpha rhythm with a great deal of widespread mixed slow activity of moderate voltage, from 2 c/s up to alpha frequency. No evident asymmetry.

X-rays of chest and hands showed no evidence of sarcoidosis.

LIST OF BOOKS RECEIVED FOR REVIEW

(As no reviewing is undertaken in the "Proceedings" this list is the only acknowledgment made of books received for review.)

Comité International de Médecine et de Pharmacie Militaire. 13me Session de Conférences du Comité International de Médecine et de Pharmacie Militaires 3–7 mai, 1950. pp. 240. Liège: Office International de Documentation de Médecine Militaire. 1952.

Daland (G. A.). A colour atlas of morphologic hematology. Edited by T. H. Ham; illustrations by E. Piotti. pp. 74. Cambridge, Mass: Harvard University Press (London: Geoffrey Cumberlege). 32s. 6d. 1951.

Keele (K. D.). Leonardo da Vinci on movement of the heart and blood. pp. 142 + xviii. 68 reproductions. London: Harvey & Blythe. £4 4s. 1952.

Northern Surgical Association. Transactions at the twenty-fifth meeting of the Northern Surgical Association held in Copenhagen June 27 to 29, 1951. pp. 460 + xvi. Copenhagen: Munksgaard. 26s. 0d. 1951.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Bett (W. R.). Osler: the man and the legend. pp. 125. London: Heinemann. 15s. 0d. 1951.

Brock (R. C.). The life and work of Astley Cooper. pp. 176. Edinburgh and London: Livingstone. 20s. 0d. 1952.

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Clarke (B. R.). Causes and prevention of tuberculosis: with a chapter on mass miniature radiography by Joseph Ritchie. pp. 288. Edinburgh and London: Livingstone. 32s. 6d. 1952.

Council for the Co-ordination of International Congresses of Medical Sciences. Symposium on geographical pathology and demography of cancer. Edited by Dr. J. Clemmesen. pp. 152. 1951.

Davson (H.). A textbook of general physiology. pp. 659. London: Churchill. 45s. 0d. 1951.

Gavey (C. J.). The management of the "hopeless" case. pp. 45. London: H. K. Lewis. 9s. 0d. 1952

Gutmann (R. A. C.), and Daoud (J.). Estomac et duodenum: introduction à l'étude radio-clinique. (3). pp. 78. Paris: Heures de France. 1951.

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Morgan (J.). The Journal of Dr. John Morgan of Philadelphia from the city of Rome to the city of London 1764. pp. 259. Philadelphia: Lippincott. 1907.

Nicolas (J.), et al. Aérosolthérapie. pp. 71. Paris: Heures de France. 1951.

Nobel Foundation. Nobel: the man and his prizes. By H. Schück *et al.* Edited by the Nobel Foundation. pp. 620. Norman: University Oklahoma Press. 45s. 0d. 1951.

Pavlov (I. P.). Павловские среды. Протоколы и стенограммы физиологических бесед (Collected notes.) 3 vols. Moskva and Leningrad: Akademii Nauk. U.S.S.R. 1949.

Weil (P.-E.), and Isch-Wall (P.). La transfusion du sang. pp. 247. Paris: Masson et Cie. 20 fr. 1925.

Section of Ophthalmology

President—W. J. B. RIDDELL, M.D., F.R.F.P.S.

[*October* 11, 1951]

"Of the Web in the Eye" [*Summary*]

PRESIDENT'S ADDRESS

By W. J. B. RIDDELL, M.D., F.R.F.P.S.

BEFORE the fall of Constantinople and when the first printed documents began to appear in Europe a University was founded in 1451 by Pope Nicholas V in the small cathedral city of Glasgow. It was laid down from the start that the methods of teaching within the University should follow those of Bologna and Paris. In the middle of the fifteenth century students followed a course of philosophy mainly in the tradition of Aristotle, but, we are told by a University historian, the students were required to study the works of Petrus Hispanus.

I have been interested in Petrus Hispanus for a number of years because he was the author of a book on diseases of the eye. In the library of Glasgow University there is a copy of this book in a fifteenth century manuscript which has some notes in the handwriting of William Hunter. The full title of the volume is "Breviarum Magistri Petri Hispani de Egritudinibus Oculorum et Curis". It is divided into five parts, an introduction, followed by an abridged version of an Arabic text, the third section is original but the fourth is a literal copy of the first book of the "Liber Oculorum" of Zacharias and a collection of prescriptions concludes the book. I like to think that ophthalmology has been studied in Glasgow for over five hundred years.

Petrus Hispanus was one of the most able persons in Europe in his time. He was born at Lisbon at the beginning of the thirteenth century and died on May 16, 1277. He was educated at Paris where he was a contemporary of Roger Bacon. In 1247 he was appointed Professor of Medicine in the University of Siena and his book on logic was used by students for over two centuries. His most famous work was his "Thesaurus Pauperum" of which an English translation was printed in 1550. This book had a wide circulation and was by far the most popular of the mediæval formularies. His treatise on "Diseases of the Eye" is a medical and literary classic. It was one of the earliest books to be written in Italian and about half a dozen manuscript copies are known to be in existence.

Petrus Hispanus is one of the three physicians who became Popes. He reigned as Pope John XXI and died from injuries following the collapse of his palace at Viterbo. Michelangelo copied out the "Liber de Oculis" for his own use and this copy is still preserved in the Vatican.

Before his accession to the Papacy he had accomplished very remarkable work in medicine and ophthalmology. Cataract is described as the "water that descends into the eye" and he makes a distinction between cataract from internal and external causes. Hardening of the eye is mentioned and this is declared to be very serious in its effects. There seems to be little doubt that this was glaucoma. He attributed squint to two causes, an affection of the eye muscle and a defect of the brain.

About 150 years after the foundation of the University in Glasgow the Royal Faculty of Physicians and Surgeons came into being as a result of the activities of Maister Peter Lowe. The charter was obtained from James VI of Scotland in 1599 and the bounds of jurisdiction were defined by an area which is for all practical purposes precisely that of the Scottish Western Regional Hospital Board of today. Lowe wrote a textbook of surgery and it is from one of the chapters devoted to diseases of the eye that I have taken "Of the Web in the Eye" as the title of this Address. He carried out couching for cataract and the instrument which he used is very similar to the needles which are illustrated in the books of today. The older writers do not always distinguish between opacity of the cornea and of the lens when they used the word web. Shakespeare uses the expression in *King Lear* "He gives the web and the pin, squints the eye, and makes the hare lip", iii, 4.

What evidence exists for the widespread belief that senile cataract is more common in India than in European countries? The number of major centres and trained ophthalmic surgeons in India is extremely small in proportion to the population which is estimated at around 400 millions. There is at present in Britain about one ophthalmic surgeon for every 100,000 of the population; a similar ratio in India would require 4,000 trained ophthalmic surgeons, and I doubt if there is anything approaching this number. Consequently, the large number of cataract operations performed in certain Indian clinics is due to the large amount of surgery requiring to be done by a small number of trained surgeons.

Some years ago, Smith of Jullunder extracted data relating to cataract from the India Office official records. These gave the annual number of cataract extractions performed in various provinces of India, excluding the work of the Mission Hospitals, over a period of years. By relating these figures to the estimated population, it can be shown that the number of cataract extractions performed per 100,000 of the population steadily increased between 1891 and 1921. This increase is most likely to be attributable to the increased efficiency of the Hospital Services, improved educational facilities, and possibly increased expectation of life. There is nothing to suggest that there has been a real increase in incidence.

These considerations led to enquiries as to the frequency of senile cataract operations in Scotland. Enquiries were made in the five Hospital Regions into which Scotland is divided for administrative purposes. They are centred on the four University Medical Schools, Aberdeen, Dundee, Edinburgh, Glasgow and on Inverness for the Highlands and Islands. The estimates were made independently by surgeons resident in the areas, and show in Table I that about 1,000 cataract operations were performed annually before the war, giving a frequency of 20 per 100,000 of the population. By applying this ratio to the whole country, an estimate may be made of the total number of cataract operations in the community at its present age structure. As the age structure of the population is altering, it is probable that during the next few decades the number of patients with senile cataract will increase. Many alarming forecasts have been made regarding this change, and the figures shown in Table II are those taken from a Report published by the Registrar-General on the *Current Trend of Population in Great Britain* (CMD. 6358, 1942). These reliable figures were prepared in order to

TABLE I.—ESTIMATED NUMBERS OF SENILE CATARACT EXTRACTIONS PERFORMED ANNUALLY IN SCOTLAND

Hospital Region	Population (in thousands)	Senile cataracts	Estimated by
N.-E.	450	70	Beatrix Law
E.	400	90	A. A. B. Scott
S.-E.	1,100	205	H. M. Traquair
W.	2,800	580	W. J. B. Riddell
N.	190	45	T. Chalmers
Total	4,940	990	

Proportion 20 per 100,000 (all ages)

TABLE II.—AGE DISTRIBUTION OF THE POPULATION IN GREAT BRITAIN (IN THOUSANDS)

Year	Age groups 45 to 64	65 and over	Total
1921	8,210	2,584	10,794
1931	9,638	3,318	12,956
1941	10,689	4,326	15,015
1951	12,061	5,511	17,572
1961	13,339	6,490	19,829
1971	13,332	7,863	21,195

Figures taken from Registrar-General CMD. 6358, 1942.

TABLE III.—ESTIMATED NUMBER OF CATARACT EXTRACTIONS IN GREAT BRITAIN

Year	Number
1921	7,671
1931	9,440
(1939)	(10,000)
1941	10,042
1951	12,214
1961	14,078
1971	15,971

TABLE IV.—VITREOUS LOSS

Series	Intracapsular No loss	Intracapsular Loss	Extracapsular No loss	Extracapsular Loss	Total
1st	68	4	28	–	100
2nd	54	1	44	1	100
3rd	58	2	40	–	100
4th	62	1	37	–	100
5th	79	2	17	2	100
Total	321	10	166	3	500

refute mere speculation concerning the age structure. From these data, it can be seen that there will be twice as many people of 45 and over in 1971 as there were in 1921, and an even higher proportion of persons over 65. The mean age of operation for cataract is about 67. In Table III the estimated number of cataract extractions in Great Britain is shown for the decades 1921–1971. These figures are calculated retrospectively and ahead on the assumption that 10,000 cataract operations were carried out in 1939. Thus it appears likely that the senile cataract population will increase by over 50% on the 1941 figure during the next twenty-five years.

There is a practical aspect to this matter which may easily be overlooked in designing hospital accommodation. The Registrar-General does not give the figures for the different sexes over 65, but it is quite certain that there will be a large excess of women. It will follow that more beds for female cataract patients will be required than for males. I have had the experience in my own Department, where the number of beds allotted to each sex is equal, of having to discontinue the admission of male patients in order to use the beds for the excessive number of female cataract patients on my waiting list. If the male and female wards are separated by a series of single or private rooms, the

difficulty can be solved easily, but if, as in my case, the male and female beds are on different floors, the problem is not so simple. The single floor system providing a shuttle service, or overlap, may be found extremely useful when the sex ratio of a waiting list presents a problem.

The results from the couching operation for cataract cannot have been universally bad. I find that in the Glasgow Eye Infirmary one hundred years ago about 20% of patients with cataract had the operation of reclination or displacement performed. The exact figures for the decade 1850–1859 were: extractions 76, reclinations 21, total 97. During the same period 426 operations of division were carried out. There is no indication of the age of these patients and consequently it is impossible to say how many of these were for congenital cataract. In the early reports of the Infirmary the number of needlings carried out on each patient is stated but this practice was discontinued after 1827.

Now, until about two hundred years ago, this method of displacing the lens into the vitreous was carried out deliberately by inserting a needle just behind the ciliary body and dislocating the lens backwards. This procedure has been carried out for thousands of years, and it would not surprise me to learn that the majority of operations for cataracts in the world were still carried out in this manner. My reason for this statement is that, if the peasant populations of Africa, India, and China are considered in relation to the number of European trained doctors in these areas, it is quite possible that the primitive operation is still the operation of election by those advising the patients.

We no longer believe that couching the lens is a superior procedure to its removal, but many patients with couched lenses survive for years with useful vision. They did not all develop secondary glaucoma, but the proportion which did so was higher than those in whom the lens was removed. Hence linear extraction replaced couching at the end of the eighteenth and the beginning of the nineteenth centuries. In those days, the majority of surgeons, particularly in the Continent, made the incision below, and this procedure lingered on until about fifty years ago.

In 1884 we find Charles Higgens reporting the results of two hundred operations. He carried out an oblique corneal section in 24 cases, a lower section in 55 and the more satisfactory upper section in 121. He thought that the iridectomy should be narrow and he did not aim to make a conjunctival flap, although he had no objection to it if the conjunctiva stretched over his knife. Loss of vitreous occurred eight times. He remarks that in the majority of the cases the section was made upwards, but when operating without anæsthetic or in cases where he expected any difficulty he made it downwards. Within six months of the publication of this paper ophthalmic surgery was profoundly affected by the introduction of cocaine in October 1884.

In the same year McKeown introduced his method of irrigating away cortical remnants with a stream of water. Pridgin Teale, in his Bowman Lecture in 1893, reported 89 extractions without iridectomy and in which vitreous was lost in 3 cases. Swanzy during the same year reported upon one hundred combined extractions in which vitreous was lost twice. In 1904 Maddox described a special needle for suturing the conjunctival flap after cataract extraction.

Steps in the evolution of an operation are easily forgotten, and it was of interest to read that at the end of last century many cataract operations were performed with a downward section following a preliminary iridectomy. As far as I am aware, the downward section is entirely abandoned, and I have never seen it carried out. I have been told of a case which occurred about 1912, where the surgeon, having inserted his knife with the cutting edge downwards, continued the section towards six o'clock, and justified the manœuvre by stating that he had learned it from his father, who was an ophthalmologist. In a paper published early this century, Andrew Wilson remarks that some operators prefer to operate by a downward section when carrying out a simple extraction, holding that a corneal wound in that position enabled them to operate with greater facility, and allowed of more easy and careful inspection of the wound during the process of healing. He personally preferred the upward section.

I do not think that anyone uses an inferior section to-day, and I imagine that it arose owing to lack of adequate anæsthesia. Our sturdy ancestors, having their cataracts removed without an anæsthetic, might well tend to roll their eyes upwards, which would make the lower section more simple to carry out. In the early days of cataract extraction, there were those who made a lateral section, and I shall not be surprised to hear of some enthusiast advocating that such a procedure is a good one and, along with a large canthotomy, claiming priority for an abandoned discovery.

My own practice is to attempt a corneo-scleral section with a conjunctival flap about 5 mm. in length and as wide as my section permits. If the corneal circumference is imagined to be divided into sixteen equal parts, I attempt to include seven of them in my section. This section may be considered to be on the small side to-day, but it has the merit that little astigmatism arises, prolapse of the iris is rare, and sutures are not required to retain apposition.

When I began to operate by the intracapsular method some years ago I made a consecutive record of all my cataract operations. The first 500 in this series is shown in Table IV with particular reference to loss of vitreous. These figures are reasonably good and I would like to pay a tribute at this point

to the fifteen surgeons at Moorfields and in Glasgow for whom I worked for periods of two years or more and who taught me their craft. I was brought up to regard loss of vitreous as a major disaster and I still hold that view. I have thought seriously that when my figures for this complication increase significantly it would be an index that my days for operating were drawing to a close. It is, of course, true that senior people have more complicated and difficult cases to deal with but we should not delude ourselves by such thinking. Loss of vitreous *is* a major disaster and the eye in which it occurs comes to no good.

After the completion of a cataract section the anterior chamber is only relatively empty. There is a residual aqueous remaining which lies mainly behind the lens, but the small quantity in front permits the use of a cystotome without entanglement of the iris. The quantity lying between the posterior lens capsule and the vitreous face acts as a synovial fluid and facilitates tumbling or rotation of the lens in the intracapsular operation. Complex manœuvres designed to ensure closure of the wound may lead to an increased frequency of vitreous loss by expelling this useful safeguard. I am satisfied that the concept of the residual aqueous is a useful one.

In a recent review of *Eye Surgery* by Stallard, written by Lawrence Post (*Amer. J. Ophthal.*, **30,** 148, 1947), the comment is made that American surgeons may be somewhat surprised that the method of corneal section with scissors for cataract extractions, now so popular in that country, is not mentioned except as an adjunct when too small a section is made with a cataract knife. Now this important change in operative technique is widely used in America, and it is one well adapted for statistical treatment. It is really a reversion to the methods used a hundred years ago, but the object is different. In order to remove the lens within its capsule intact, a larger section is said to be required than in the extracapsular operation. The larger section involving almost half the cornea is excessively difficult to carry out with a Graefe knife whilst avoiding the iris. The introduction of a larger section increases the likelihood of the wound opening, iris prolapse, and vitreous loss. Increased frequency of vitreous loss may be inherent in the intracapsular operation as the posterior lens capsule is not retained as a support. In order to be in a position to deal with these complications, should they arise, a variety of wound sutures have been introduced. The technical advance in suture manufacture, and the introduction of fine eyeless needles, has made these procedures technically simple.

It would appear to be necessary to show that the more elaborate procedures have a positive advantage over the less elaborate. This can only be a statistical answer. The methods themselves are within average competence, and indeed it might be claimed that the external approach, followed by a keratome section enlarged with scissors, is, in fact, an easier method for the beginner than the attempt to make a large section with a Graefe knife. We may easily forget the evolution of our own experience and the steep mental ladder which has to be climbed before any operative technique can become integrated within our thought.

The following is a quotation taken from the Inaugural Address delivered by Sir James Learmonth, when he came from the Mayo Clinic to occupy the Chair of Surgery in The University of Aberdeen:

"The acquisition of surgical art is one of the most valuable products of experience; and in experience is included not only personal experience, but also familiarity with the writing and with the practice of the Masters of our profession. To a fortunate few, surgical judgment seems to come early and without effort. For the majority the development of surgical art is at first a conscious process and each necessity for displaying it entails the deliberate weighing of all immediate and remote factors bearing upon the problem. As experience increases, decisions are reached by mental short-cuts, and to me the supreme intellectual satisfaction in the practice of surgery is the realization, as occasion arises, that a decision which proves to be correct has required no laborious process of integration. That most philosophic of surgeons, Sir Benjamin Brodie, put the matter thus: 'I cannot well understand what I observed to happen in myself without supposing that there is in the human mind a principle of order which operates without the mind itself being at the time conscious of it. You have been occupied with a particular investigation; you have accumulated a large store of facts, but that is all. After an interval of time, and without any further labour, or any addition to your stock of knowledge, you find all the facts you have learned in their proper places, although you are not sensible of having made an effort for the purpose.' It may be added that these words are applicable to the whole field of intellectual endeavour and not to surgery alone, although they have a special significance in the field of biological research."

Much has been and will be written regarding the technique of carrying out all operations, but that for the removal of the crystalline lens has almost certainly received more detailed study than any other operative procedure. My famous predecessor, William Mackenzie, was well aware of this over a hundred years ago. The following quotation from the second edition of his "Diseases of the Eye" (p. 705, 1835, London) brings out my point.

"The instruments invented for the performance of the operations for cataract are infinitely various, almost every operator, and in many instances those who have operated little or none, have modified the old or invented new ones. The simpler and the fewer the instruments are, the better. If the young oculist attach himself to the simplest modes of operating, and acquire dexterity and skill in their performance, he will think little of the complicated contrivances with which some have tried to make up for their want of knowledge, and their deficiency in mechanical adroitness."

[*December* 13, 1951]

DISCUSSION ON THE MANAGEMENT OF ENDOCRINE EXOPHTHALMOS

Dr. **Russell Brain**: The following observations are based on over 150 cases.

Ætiology

There is no evidence that thyroxin can cause exophthalmos, though it may produce lid retraction. It is probable, though not yet proved, that the exophthalmos both in Graves' disease and in exophthalmic ophthalmoplegia is due to the thyrotrophic hormone of the pituitary. Both diseases should then be regarded as disturbances of the thyroid-pituitary axis with the possible intervention of the hypothalamus. It is suggested that normally there is a balanced relationship between the secretion of thyroxin by the thyroid and the production of thyrotrophic hormone by the pituitary, that in exophthalmic goitre this mechanism is still working but set at a higher level for thyroxin production as a thermostat might still be regulating the temperature though the room was kept too hot, whereas in exophthalmic ophthalmoplegia the production of the thyrotrophic hormone is no longer under control. This may happen when existing thyroid activity is suddenly depressed either by removal of part of the gland, or by the use of antithyroid drugs, or when a primary stimulus to the pituitary-thyroid axis finds an active pituitary with a relatively unresponsive thyroid.

Prognosis

In considering the effects of various methods of treatment it is necessary to take into account natural variations in the course of the disease and the inconstant response to treatment. There is an exception to every statement that can be made about exophthalmic ophthalmoplegia. In cases treated medically I should estimate the prognosis as follows:

	%
Almost well	5
Much improved	15
Improved	20
Unchanged..	45
Worse	15

I have never seen complete recovery. Since widespread fibrosis develops in the orbital tissues in the untreated case, much less improvement can be expected in long-standing cases than in cases treated early.

Treatment

Treatment may be called for on account of the patient's complaint of (1) exophthalmos, (2) double vision, (3) the threat of danger to the cornea, or (4) to the optic nerves through papillœdema or primary optic atrophy. (5) Associated thyrotoxicosis may call for treatment, or (6) associated myxœdema, while, rarely, there is (7) associated myasthenia.

Treatment may be directed to (1) diminution of pituitary secretion. (*a*) Administration of thyroid extract should theoretically accomplish this, but I have been disappointed in its use. (*b*) The same applies to ovarian follicular hormone and testosterone. Sometimes stilbœstrol seems to be of benefit and I have used it in increasing doses up to 10 mg. daily for two or three months at a time, but often it appears to do no good. (*c*) X-ray irradiation of the pituitary, though, again, often disappointing, in some cases seems to give more satisfactory results than any other form of treatment. (2) Treatment of the orbital contents. X-ray irradiation of the orbit has its advocates, but it must be difficult to distinguish between this and irradiation of the pituitary. Surgical decompression of the orbit is called for when severe exophthalmos cannot be otherwise controlled, when the cornea is threatened and in the presence of papillœdema or primary optic atrophy. It usually saves the situation, though, occasionally, even this method of treatment fails. (3) ACTH and cortisone. American reports on the use of these preparations have not been encouraging, but Drs. G. N. Chandler and S. J. Hartfall allow me to say that they have recently used cortisone in three cases and ACTH in one and both in a fifth with results sufficiently encouraging to justify further investigation. (4) Prostigmin. I have never seen benefit derived from this. (5) Treatment of associated thyrotoxicosis. This constitutes one of the most difficult of therapeutic problems. Occasionally severe thyrotoxicosis calls for urgent treatment, especially if it is causing auricular fibrillation. Sudden diminution of the thyrotoxicosis either by operation or by antithyroid drugs may be followed by rapid intensification in the exophthalmos. In my experience this is most likely to happen in males with thyrotoxicosis and disproportionately severe exophthalmos and pink congested conjunctivæ. Usually these patients have not got ophthalmoplegia. Where exophthalmic ophthalmoplegia is of six months or more duration, the risks of dealing with the thyroid seem to be less. In such cases I prefer iodine and surgery to the antithyroid drugs. (6) Treatment of associated myxœdema. It is usually safe to treat the myxœdema with the usual doses of thyroid extract, though I have had one patient who developed a sustained thyrotoxicosis after that treat

ment. (7) Treatment of associated myasthenia. These cases are too rare for me to discuss them in detail. Zondek, H., and Ticho, A. (1951, *Lancet*, ii, 1018), report successful treatment of both the exophthalmic ophthalmoplegia and the myasthenia by X-ray irradiation of the pituitary. (8) Amelioration of end-results. Most patients are left with some persistent ophthalmoplegia. Mr. Arthur Lister (personal communication) has diminished diplopia by operations on the eye muscles, his work suggesting that failure of the opposing muscles to relax may be an important factor in limiting movement. If the staring appearance of the eye distresses the patient, lid retraction may be diminished by cervical sympathectomy.

Mr. T. Keith Lyle: The chief ocular complications of endocrine exophthalmos which require special consideration and treatment are three in number and appear to be due to increased orbital tension: (1) Corneal ulceration due to defective eyelid closure resulting from severe exophthalmos. (2) Defective vision due to circulatory disturbances involving the optic nerve. (3) Diplopia due to ocular muscle palsies caused by cellular and œdematous infiltration of the ocular muscles, with subsequent fibrosis.

A minor complication of rare occurrence and one of no serious significance consists of an alteration in refraction (especially in corneal astigmatism).

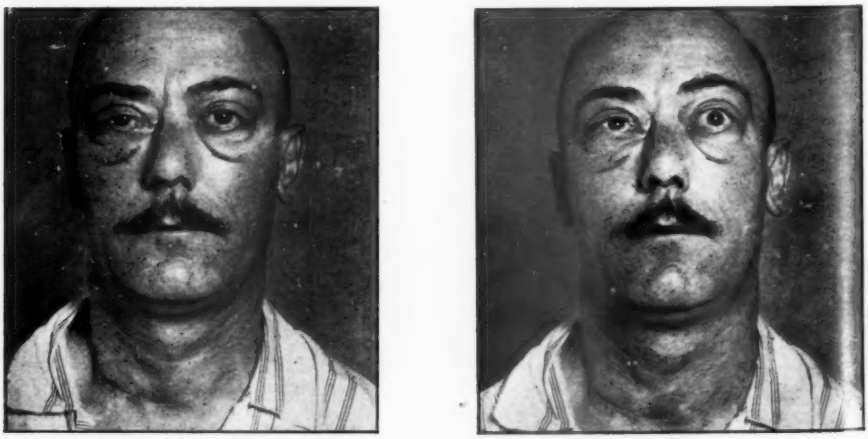
(1) *Defective Eyelid Closure*

This may result in chemosis and drying of the exposed conjunctiva and of the cornea with subsequent ulceration. The latter may be accompanied by hypopyon and iritis and may lead to panophthalmitis with or without perforation of the ulcer and loss of the eyeball. These complications should in most cases be prevented by adequate tarsorrhaphy performed in the early stages, and also, when necessary, by early orbital decompression. Unfortunately such measures are too often postponed until too late. An alternative method of dealing with increased orbital tension is by means of deep X-ray therapy applied to the orbits and to the pituitary gland (Paufique).

(2) *Defective Vision Due to Circulatory Disturbances of the Optic Nerve Caused by Increased Orbital Tension*

(*a*) There may be *œdema of the optic disc* (choked disc) due presumably to interference with the venous return from the eyeball via the central retinal vein. In this condition the visual defect may be slight, on the other hand it may be considerable if the pressure has acted sufficiently long and has been of such severity as to cause atrophy of some of the optic nerve fibres. The following case illustrates this:

A. F., male, aged 42. September 1949: Thyrotoxic symptoms (dyspnœa, loss of weight, nervousness, B.M.R. + 29%) treated with thiouracil for six months—no improvement. November 1950: Subtotal thyroidectomy. Fifteen days after operation his eyes became prominent and his vision began to deteriorate rapidly. April 1951 (under the care of Mr. Frank Law): Bilateral tarsorrhaphy and excision of some orbital tissue. July 1951: Occasional vertical diplopia on looking upwards. Admitted to National Hospital, Queen Square, August 1951 (under the care of Dr. S. P. Meadows). Defective upward movement of both eyes, bilateral exophthalmos with orbital œdema (*see* Fig. 1).



(*a*) (*b*)

FIG. 1.—Bilateral exophthalmos with defective upward movement of both eyes. (*a*) Eyes in primary position. (*b*) Eyes in position of maximum elevation.

Gross bilateral optic-disc œdema of the chronic type with some greyness of the discs. Vision uncorrected 1/60 each eye. August 14 and 24, 1951: Lateral decompression of right and left orbits respectively by Mr. Harvey Jackson, who found the orbital fascia on both sides to be tense and the contents of both orbits firm and swollen.

A portion of the left lateral rectus was taken for pathological examination. It showed "extensive replacement of muscle fibres by connective tissue. Some enlarged muscle fibres with large hyperchromatic nuclei and cytoplasm staining less deeply than normally. Small round cell, plasma cell, and occasional polymorphonuclear cell infiltration around nerve fibres and blood vessels".

The degree of swelling of the optic disc has so far remained unchanged, although the ocular movement has improved and the proptosis has decreased. When last examined December 1, 1951, his vision was:

Rt. $\bar{c}+5{\cdot}50$ / $+3{\cdot}00$ axis $100°$ = 6/18, and J4 with + 1·00 added

Lt. $\bar{c}+5{\cdot}00$ / $+4{\cdot}50$ axis $75°$ = 6/18, and J4 with + 1·00 added

Maddox Rod test at 6 metres, Eso. 5$^{\Delta}$, R/L 3$^{\Delta}$. Visual fields showed enlargement of the blind spots with a scotoma in the centrocæcal area each side.

Another case of exophthalmic ophthalmoplegia with optic disc œdema was a woman aged 46 whose exophthalmos greatly increased one month after subtotal thyroidectomy for thyrotoxicosis. Three months later she complained of defective vision. Her corrected vision was 6/12 and J2 in the right eye and 6/24 and J2 in the left eye. She had bilateral optic disc œdema with about 2 dioptres of swelling with several small hæmorrhages at the disc edge. The swelling of the disc has subsided slightly but her vision is unchanged. Orbital decompression was not carried out in this case.

(*b*) There may be *ischæmia of the optic nerve* involving the central vessels at the nerve head, or involving the smaller vessels supplying the optic nerve further back in the orbit.

I have seen 2 cases of this apparent ætiology. The first was a man aged 55 who had a subtotal thyroidectomy for thyrotoxicosis in 1947, followed by increasing exophthalmos necessitating orbital decompression in 1948. He complained that his sight was defective. V.A. was 6/9. There was pathological pallor of both optic discs.

The second was a woman, aged 40, who had had a subtotal thyroidectomy for thyrotoxicosis in 1948 followed by increasing exophthalmos necessitating orbital decompression. In spite of energetic treatment the left eye was subsequently lost, due to panophthalmitis, resulting from corneal ulceration. The right eye showed pathological pallor of the optic disc with vision of 6/12. There was a small paracentral scotoma with constriction of the temporal field.

(3) *Diplopia Due to Ocular Muscle Palsies*

The ocular muscles appear to be affected by œdema, round-celled infiltration, degeneration and fragmentation of muscle fibres with much swelling, and later with interstitial fibrosis. In some cases the changes appear to affect all the muscles to a more-or-less equal extent, with the result that there is merely a slight interference with the full range of ocular movements, but no obvious symptoms. In other cases the onus of the palsy appears to fall mainly upon one muscle of one eye only or upon one muscle of both eyes, usually to an unequal extent with resulting diplopia. In these cases the muscle most often affected is the superior rectus.

In some cases there is a gross and widespread defect of ocular movement, which appears to be mainly owing to a fibrotic condition of several of the muscles. In the most severe cases the eyes become almost fixed in a deviated position, due largely to fibrous changes in all the extrinsic ocular muscles.

Thus, cases of ocular muscle palsy due to endocrine exophthalmos may be divided into three types: (1) Those in which there is a defect of ocular movement, but a defect which is symmetrical and equal and which therefore does not give rise to diplopia. (2) Those in which the onus of the palsy appears to fall mainly on one muscle—usually the superior rectus—with proptosis of moderate degree. (3) Those in which there is a gross defect of ocular movement in almost every direction, with marked proptosis. In some cases in this third group the eyes become almost fixed in a convergent and sursumvergent position, having the appearance of "strabismus fixus".

In the majority of these cases in which diplopia exists it can be overcome by appropriate ocular muscle surgery, which, however, should not be undertaken until the patient's general condition is satisfactorily stabilized.

It is well recognized that the disease appears eventually to be a self-limiting one, as exemplified by the following case:

In 1936, E. W., aged 37, developed vertical diplopia a few days after a subtotal thyroidectomy for thyrotoxicosis, with marked proptosis. When examined one month later he had paresis of the right superior rectus with 17$^{\Delta}$ of right hypotropia (Maddox Rod test at 6 metres). Thirteen years later his right hypotropia was precisely the same, i.e. 17$^{\Delta}$, and the defective movement of the right eye was as before. He had had no treatment in the intervening period with the exception of prismatic spectacle lenses to correct two-thirds of the deviation, which overcame the diplopia. The spectacles had not been altered for thirteen years.

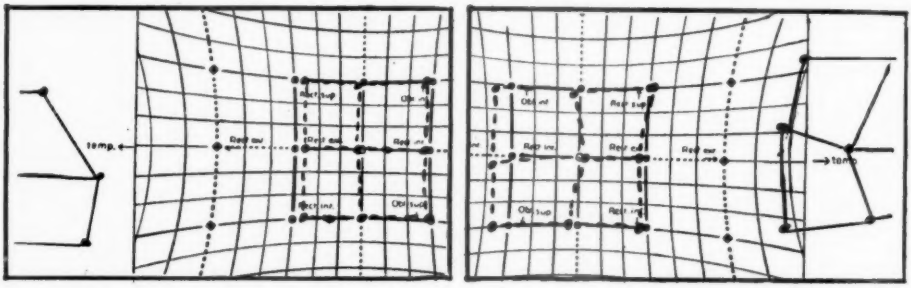
Treatment

In contra-distinction to cases of ocular muscle palsy due to a lesion of the nerve supplying the muscle, these cases do not show the typical overaction of the contralateral synergist. Thus, in a case of superior rectus palsy it is of little value to myectomize the contralateral inferior oblique. In cases of moderate severity a resection of the affected muscle may suffice, but in those of greater severity a recession of the direct antagonist is indicated also. Although from the clinical point of view it may appear obvious that there is, say, defective dextro-elevation of the right eye, it may not be correct to draw the conclusion that there is a primary paresis of this muscle; it is quite possible that the paresis is secondary to a state of contracture of the right inferior rectus. In some cases evidence of this can be demonstrated by means of examination with the Hess Screen.

The following are typical examples of cases of exophthalmic ophthalmoplegia in which diplopia has been overcome by operation upon the extrinsic ocular muscles:

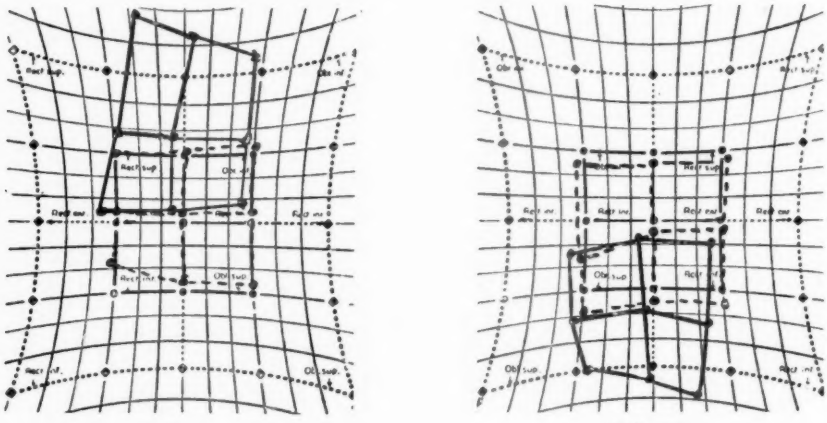
Case I.—Mrs. O. T., aged 30, had a gradual onset of proptosis and double vision in September 1949. She had a left esotropia of 48$^{\Delta}$ and a left hypertropia of 13$^{\Delta}$. There was gross weakness of elevation and, to a less extent, of depression of both eyes. She also had a bilateral palsy of the lateral recti. Operation was carried out in three stages: First, a recession of the left medial rectus and a resection of the left lateral rectus, then a recession of the right medial rectus, and finally a recession of the left superior rectus and a resection of the left inferior rectus.

Orthophoria was obtained in the primary position, with complete freedom from diplopia. Fig. 2 shows the pre- and post-operative Hess Charts.



Left eye. Right eye.

Fig. 2 (*Case I*).—Hess Charts: Pre-operative—continuous line; Post-operative—interrupted line.



Left eye. Right eye.

Fig. 3 (*Case II*).—Hess Charts: Pre-operative—continuous line; Post-operative—interrupted line.

The pathological report (Professor H. A. Magnus) upon portions of the left superior and left inferior rectus removed at operation was as follows:

(*a*) Section of the *superior rectus muscle* shows fibres of a uniform size, though some are a little swollen. Many fibres show patchy degenerative changes with loss of transverse striation, and vacuolation. There is some multiplication of the sarcolemmal nuclei. There is no fibrosis or cellular infiltration. Section of Tenon's capsule

and orbital fat shows fibrous and adipose tissue. There are no pathological changes, apart from congestion and hæmorrhage which are presumably of operative origin.

(*b*) Section of the *inferior rectus muscle* shows fibrous tissue only.

Case II.—Mr. C. B., aged 39. He had had a left orbital decompression previously. There was no antecedent history of thyroid disease. Ocular symptoms dated from 1943 and consisted of proptosis and diplopia. He had paresis of elevation of his right eye and of depression of his left eye with a left sursumvergent squint of 36^.

Operation was carried out in two stages. First a recession of the left superior rectus, and second a marginal myotomy of the right inferior rectus. Fig. 3 shows the pre- and post-operative Hess Charts.

Case III.—Mr. H. S., aged 50, was a more complicated problem in that he had practically no ocular movement, and his eyes were fixed in a position of elevation, necessitating the adoption of a compensatory head position consisting of extreme depression of the chin in order to see where he was going. He had been on thiouracil treatment for thyrotoxicosis in 1948 and subsequently developed proptosis and diplopia. The problem here was largely a matter of how to provide him with a pair of eyes whose visual axes were parallel and directed straight ahead. This was achieved by means of a recession of both superior recti and a resection of both inferior recti.

Acknowledgments.—I am indebted to my colleagues, Dr. S. P. Meadows and Mr. Frank W. Law, for permission to refer to their cases.

Dr. K. Aterman (Birmingham) said that a short statement of some of his preliminary findings on the experimental production of exophthalmos had appeared in *Brit. med. J.*, 1951, ii, 609. He had found that whereas a moderate degree of protrusion of the eyeballs could be produced by thyrotrophin alone, exophthalmos appeared to develop more rapidly and to become more marked in cortisone-treated guinea-pigs. The literature on the subject showed that several cases of exophthalmos had developed rapidly after infection or trauma. A case had been shown in the Section of Pædiatrics of a child whose exophthalmos had become worse after tonsillitis (Weller, S. D. V., *Proc. R. Soc. Med.*, 1951, **44**, 733).

As to the use of ACTH in the treatment of exophthalmos Dr. Aterman quoted the case of Zondek, H., and Ticho, A. (1951, *Lancet*, ii, 1018), where the proptosis appeared to get worse after ACTH, but improved after irradiation of the pituitary. Woods, A. C. (1951, *Amer. J. Ophthal.*, **34**, 945), concluded that, so far, there was no evidence of an effect of cortisone on exophthalmos, although the chemosis and inflammation responded well. It seemed to Dr. Aterman that one had to distinguish between these two aspects. As far as exophthalmos in primary myxœdema was concerned these cases were extremely important since they could help to throw some light on the part played by thyrotrophin and/or cortisone in the production of exophthalmos. He would be grateful if members of the audience could kindly let him have details of such cases.

Mr. J. H. Mulvany: Although the conception of hyperthyroidism as a single unit depending upon thyrotrophic activity finds favour with many, there would nevertheless appear to be grounds for splitting the hyperthyroid complex into at least three groups.

The first and largest comprises *thyrotoxicosis* (Graves' disease). Its causation is unknown but would seem to be independent of thyrotrophic activity. Autopsy in persons dying from typical Graves' disease discloses usually a small pituitary, the cells of which are also small and filled with granules, while there is increased intercellular spacing suggestive of subactivity. Other indications of pituitary hypofunction are seen in the wasting of the adrenal cortex, degeneration of the islets of Langerhans and the relative inactivity of the gonads. No excess of thyrotrophic hormone is detectable in the serum, even in the most toxic states, a circumstance rather naïvely explained by the hypophyseal protagonists as being due to its immediate utilization by the thyroid gland. The failure to detect a pronounced rise after thyroidectomy is not explained at all. In short, there is no real evidence at present to implicate the pituitary gland in the causation or maintenance of thyrotoxicosis.

On the other hand, the second and smaller hyperthyroid group is *thyrotrophic* in origin. Occurring physiologically in pregnancy, as a transient menstrual phase, and in certain puberty goitres, and pathologically in acromegaly, the hyperthyroid symptomatology differs from the thyrotoxic mainly in its relative mildness, in the slight degree of associated sympatheticotonia, in the tendency to spontaneous remission and in the constant presence of detectable quantities of thyrotrophic hormone. Thyrotrophism, i.e. the state of increased thyrotrophin in the circulation, is also seen without hyperthyroidism in the thyrogenous type of myxœdema as opposed to that form of thyroid deficiency resulting primarily from pituitary failure.

Lastly, there is the very small and rare group of hyperthyroidism due to local thyroid disease, usually neoplasia, which may be termed *thyropathic*. All types of endocrine neoplasia may give rise to increased or perverted hormonal secretion. Common examples are seen in the tumours of the adrenal medulla and cortex, of the gonads and in the insulin-secreting pancreatic adenomata. In some instances of thyropathic hyperthyroidism, the basal metabolism may remain elevated, after thyroidectomy, by the secondary deposits.

Of these various forms of hyperthyroidism, two only are associated with exophthalmos, namely, thyrotoxicosis proper and one variety of thyrotrophic hyperthyroidism which may suitably be termed exophthalmic thyrotrophism, indicating thereby not only the pathogenesis of the disease but also its point of difference from the other members of the thyrotrophic group. The proptosis of the first group is essentially thyrotoxic, that is to say, it arises from the combined effects of hyperthyroidism and

sympatheticotonia, the two essential components of the disease. On the other hand, thyrotrophic exophthalmos is completely unrelated to any hyperthyroidism with which it may be associated, its origin depending upon a local interaction of the thyrotrophic hormone and one other factor which may be a steroid compound, as suggested by the speaker some twelve years ago (Mulvany, 1944). The operation of an additional factor is evident from the fact that proptosis does not develop in the other forms of thyrotrophism.

In thyrotoxicosis, the most important factor in the development of exophthalmos is the progressive loss of tone and strength in the voluntary eye muscles whereby the power which retains the globe within the orbit is reduced. The weakness is due partly to local neuromuscular degeneration and partly to thyrotoxic myasthenia, the latter feature being a constant accompaniment of thyrotoxicosis. It is the uneven development of this muscle weakness which may lead to irregular eye movement and sometimes to a palsy, the designation of which should be thyrotoxic ophthalmoplegia. In such instances, the myasthenic characteristic of improvement after rest or following Prostigmin administration may be observed and benefit follows thyroidectomy.

Of importance also in the development of thyrotoxic proptosis is spasm of the unstriped musculature of the front half of the orbit resulting from sympatheticotonia. This muscle stretches in the form of a circle from the region of the periorbital septum anteriorly to the equator of the globe where it is attached to the tendinous insertions of the recti muscles. It is thus in a position to exert a forward pull on the globe and, in the presence of the weakened eye muscles, gradually draws the organ forward through the widened palpebral fissure. Rundle and Pochin (1944) have demonstrated the presence of an increased quantity of intra-orbital fat and have suggested that this may be the cause of the proptosis. A good part of this fat is derived from the fatty degeneration and infiltration of the muscles which are not, in this form of exophthalmos, noticeably increased in size. At the same time, the proptosis is not accompanied by signs of increased retrobulbar pressure. Nevertheless, the effect, if significant, would tend to reinforce the forward pull of the unstriped muscle. Weakness of voluntary musculature is still essential.

Treatment of this form of proptosis must depend primarily upon control of the excessive thyroid secretion. Ulceration resulting from lagophthalmos is rare to-day but responds well to tarsorrhaphy in view of the general absence of marked lid tension. Persistent marked exophthalmos after thyroidectomy may be modified by apposition of the lids at the outer canthus.

Thyrotrophic exophthalmos on the other hand presents a different problem. The mechanism is formed by the progressive enlargement of the intra-orbital muscles and treatment must be directed to the control or accommodation of this expansion. Many cases respond to indirect thyrotrophic control by means of thyroid/iodine administration, the earlier ones with less fibrotic changes in the eye muscles being more likely to respond.

Medical treatment must be prolonged and constant, how much so may be estimated from observation of this form of therapy in other endocrinal fields. For the past five years now the speaker has employed various combinations of thyroid, iodine and di-iodotyrosine as a means of œstrogenic control, and some half-dozen gynæcological and obstetrical states have been found to respond. For instance, 85% of cases of uterine bleeding without apparent local disease can be cured by this treatment. It was observed, however, that only 34% improved after four months and some cases required up to one year's treatment. Similarly in thyrotrophic exophthalmos the output of thyrotrophin can be lessened only slowly by this indirect form of therapy, and in the more acute type of case it may not be wise to rely upon it. Unless urgent, however, this type of treatment should receive a trial. Pituitary irradiation has proved successful as Mr. F. Juler's case amply demonstrates. The danger of hormonal side-effects, however, must be borne in mind. The use of testosterone is inadvisable in view of the likelihood of the steroids being concerned in the causative mechanism.

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Mr. Kenneth C. Wybar (Glasgow) said that he had been interested in Dr. Aterman's finding that cortisone increased the degree of experimental thyrotrophic exophthalmos. Jefferies (1949) had tried to produce exophthalmos with ACTH but without result. Similarly Smelser and Ozanics (1951) had obtained a negative result with ACTH and cortisone. All these workers used guinea-pigs.

On theoretical grounds one might expect cortisone to *reduce* the degree of developing thyrotrophic exophthalmos by decreasing the volume of new tissue within the orbit.

In some recent work he had been doing on the effect of cortisone on corneal vascularization, he had found an entirely different result in the guinea-pig as compared with the rabbit. It is known that there is a definite species difference in the response of animals to cortisone. Cortisone may have, therefore, a different influence on thyrotrophic exophthalmos in animals other than the guinea-pig.

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Mr. E. F. King said that temporary tarsorrhaphy was a most important measure in some cases. To secure adequate covering of the eye a generous external canthotomy should be done and the outer third of both lids freely mobilized by dividing their attachments to the orbital margins. A mattress suture would keep the lid margins in apposition for some days, after which it could be reinserted. In this way it was possible to keep the cornea covered by the lids for several weeks, often with the utmost benefit to its nutrition.

Mr. Anthony Hollingsworth said that it was possible to do a very simple decompression of the orbit by making an incision as one did for an inferior oblique myomectomy. A slight decompression of the orbit was obtained in that way. A case he had recently dealt with by that means had shown a slight improvement. Only two or three stitches in the skin were needed.

Mr. Frank W. Law endorsed what the last speaker had said with regard to transconjunctival decompression. In his own experience it was extremely effective. Apart from this, he had nothing to add with regard to orbital decompression for reducing the contents of the orbit, but he was seriously worried as to the effect of orbital decompression in cases of swelling of the optic nerve-head. He was unable to explain how the orbital contents under pressure could produce papillœdema, and was troubled by the almost constant depression of vision which accompanied it. Such cases were rare, but they were most important. Did others share his view that, for swollen optic nerve-head, decompression was of no use? Certainly he had been most disappointed by his own experience.

Mr. Harold Ridley said that limited elevation was almost invariably the main defect of ocular movement. He thought that this was due not primarily to weakness of the superior rectus but to contracture of the inferior rectus. In the active phase muscle biopsy had revealed the presence of masses of lymphocytes while in the chronic phase fibrosis occurred. At operation he had found the inferior rectus shrunken and extensively adherent to the sclera. These findings suggested that exophthalmic ophthalmoplegia might be caused by an inflammatory condition affecting mainly structures in the lower part of the orbit rather than a palsy of elevating muscles. Conjunctival œdema which was also a constant feature in severe cases in the active phase might also be due in part to local inflammatory processes.

Mr. T. Keith Lyle, speaking on decompression of the orbit in order to improve vision, said he entirely agreed with Mr. Law; he, too, had seen no improvement in vision as a result of decompression of the orbit.

In reply to Mr. Harold Ridley it was impossible to say definitely whether the apparent paresis of the superior rectus was a primary condition or whether it was secondary to fibrosis of the antagonistic inferior rectus. It is possible that one or other factor only may be present, or in some cases both factors. On one occasion he merely did a resection of the defective superior rectus and obtained a satisfactory result; had there been any degree of fibrosis of the ipsolateral inferior rectus it is unlikely that such a result would have been obtained.

Mr. Frank Juler showed a case which had been a severe example of endocrine exophthalmos but which had responded well after irradiation of the pituitary area.

At the age of 59 the patient, a male, developed thyrotoxic symptoms after influenza. As these did not respond to thiouracil and the usual remedies, partial thyroidectomy was performed five months later in June 1948, with relief of his toxic symptoms. No eye trouble was evident at the time, but in October ophthalmoplegia and orbital fullness were detected, with an exophthalmos reading (von Hertel) of 16. Early in March 1949 severe congestion with gross bilateral chemosis (exophthalmos reading 25) occurred and glaucoma was present (Fig. 1).

FIG. 1.—The condition on April 12, 1949, some six weeks after the onset of the acute symptoms. Exophthalmometer reading 25 R. and L. Chemosis severe. Slight improvement had begun.

Local treatment.—The retraction of the upper lids was not so tense as in some cases, and it was possible to keep the corneæ nearly covered. The eyes were protected with a vaseline dressing, were lubricated with liquid paraffin, and kept clean with simple irrigation, penicillin and proflavine drops. Eserine drops were used for the glaucoma. The corneæ did not become ulcerated.

General treatment.—At first thyroid extract was given for one week, with slight improvement but with reappearance of toxic signs (B.M.R. + 15%, pulse 100). Testosterone 25 mg. daily for fifteen days caused discomfort. Pituitary irradiation: twelve doses were given in sixteen days (six of 220 r and six of 330 r), a total dosage of 3,300 r between March 24 and April 8, 1949 (Fig. 4).

Progress.—Improvement was evident towards the end of April with diminution of chemosis and ophthalmoplegia. By the end of May the chemosis on the right side had almost gone, that on the left was slight. The ocular movements were much improved in the downward and inward direction, but elevation and abduction were defective. (Exophthalmos R. 21, L. 22, B.M.R. − 4%, pulse 80) (Fig. 2). By January 1950 the exophthalmos reading was 16.

Present condition (November 1951).—Improvement has been without relapse. Exophthalmos reading 13. No lid retraction: elevation and abduction weak; orbital resistance still present: tension controlled by pilocarpine, but vision impaired by glaucoma (R.V. 6/36, L.V. 6/9): general health excellent. (*See* Fig. 3.).

FIG. 2.—Taken on July 5, 1949, shows the diminution of the chemosis. The exophthalmometer reading was R. 20, L. 21.

FIG. 3.—Taken in February 1952: exophthalmometer readings, 13. Lids normal. Convergence from abduction defects.

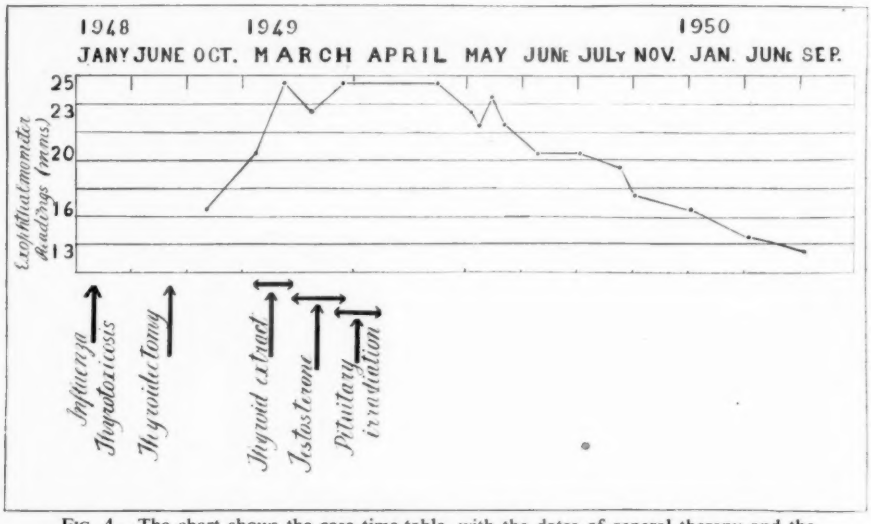

FIG. 4.—The chart shows the case time-table, with the dates of general therapy and the exophthalmometer readings.

Discussion.—Spontaneous recovery from such a severe orbital condition is unusual, and although this was a post-influenzal case, it seems probable that the pituitary irradiation supplied the stimulus necessary for the remarkable improvement which occurred. Mr. Juler had no further personal experience of this method of treatment, but from several colleagues he had received private communications relating to satisfactory results in 15 cases of varying severity. The moderate dosage necessary (4,200 to 3,300 r) appeared to be without danger when applied by the expert in radiation therapy (see Hermann, Kate (1952) *Brit. J. Ophthal.*, **36**, 1).